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(54) **NEW P2X 7 RECEPTOR ANTAGONISTS FOR USE IN THE TREATMENT OF INFLAMMATORY, IMMUNE OR CARDIOVASCULAR DISEASES**

NEUARTIGER P2X 7 REZEPTOR-ANTAGONISTEN ZUR VERWENDUNG IN DER BEHANDLUNG VON ENTZÜNDLICHEN, IMMUNINDUZIERTEN ERKRANKUNGEN ODER ERKRANKUNGEN DES HERZ-KREISLAUF-SYSTEMS

NOUVEAUX ANTAGONISTES DES RECEPTEURS P2X 7 UTILES DANS LE TRAITEMENT DE MALADIES INFLAMMATOIRES, IMMUNITAIRES OU CARDIOVASCULAIRES

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(56) References cited:
WO-A1-96/13262 **WO-A1-99/29686**

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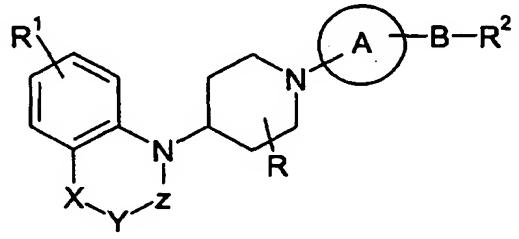
Description

[0001] The present invention relates to piperidine derivatives, a process for their preparation, pharmaceutical compositions containing them, a process for preparing the pharmaceutical compositions, and their use in therapy.

[0002] The $P2X_7$ receptor (previously known as P2Z receptor), which is a ligand-gated ion channel, is present on a variety of cell types, largely those known to be involved in the inflammatory/immune process, specifically, macrophages, mast cells and lymphocytes (T and B). Activation of the $P2X_7$ receptor by extracellular nucleotides, in particular adenosine triphosphate, leads to the release of interleukin-1β (IL-1β) and giant cell formation (macrophages/microglial cells), degranulation (mast cells) and L-selectin shedding (lymphocytes). $P2X_7$ receptors are also located on antigen-presenting cells (APC), keratinocytes, salivary acinar cells (parotid cells) and hepatocytes.

[0003] It would be desirable to make compounds effective as $P2X_7$ receptor antagonists for use in the treatment of inflammatory, immune or cardiovascular diseases, in the aetiologies of which the $P2X_7$ receptor may play a role.

[0004] In accordance with the present invention, there is therefore provided a compound of formula (I):



(I)

where

A is phenyl or a 5- or 6-membered heterocyclic ring containing one or two heteroatoms selected from O, N or S; and optionally substituted by $C_{1\text{-}6}$alkyl, halogen, nitro, amino, C_1-C_6alkylamino, CF_3, SO_2Me, $NHSO_2Me$ or cyano;

B is C=O, NH or SO_2;

X is C=O, CH(Me), O or $(CH_2)p$ where p is 0 or 1;

Y is O, CH_2, NH or S;

Z is C=O or SO_2, provided that when Z is C=O, then Y is O, CH_2 or S;

R is hydrogen or $C_{1\text{-}6}$alkyl;

R^1 is hydrogen, halogen;

R^2 is phenyl optionally substituted by CO_2H, CO_2-C_1-C_6alkyl, $CONH_2$ or R^2 is OH, NHR^3, $NHCH(R^4)(CHR^5)_nR^6$, NH-R^7-R^8, SO_2NHC_1-C_6alkyl, $NHCOC_1$-C_6alkyl, $NHSO_2C_1$-C_6alkyl, morpholine, NR^9R^{10}, piperazine substituted by phenyl,

C_1-C_6alkoxyphenyl, pyridyl or fluorophenyl;

n is 0, 1 or 2;

R^3 is hydrogen, a bi- or tricyclic saturated ring system optionally containing a nitrogen atom, piperidinyl, C_1-C_6alkylpyrrolidine, ethynylcyclohexyl, a 5-membered aromatic ring containing 2 or 3 heteroatoms, $C_{4\text{-}6}$ cycloalkyl optionally substituted by C_1-C_6alkyl, cyano or hydroxy, or $C_{1\text{-}8}$ alkyl optionally containing an oxygen atom in the alkyl chain and being optionally substituted by one or more substituents selected from ethynyl, cyano, fluoro, di-C_1-C_6alkylamino, hydroxy, thioC_1-C_6alkyl, CO_2R^{11} or $CONH_2$;

R^4 is hydrogen or C_1-C_6alkyl optionally substituted by hydroxy or C_1-C_6alkoxy;

R^5 is hydrogen or hydroxy;

R^6 is CO_2R^{11}, $NHCO_2R^{12}$, $CONH_2$ or a 5 or 6-membered saturated ring containing an oxygen atom, a 5-membered heterocyclic ring containing one or two heteroatoms selected from O, N or S, or phenyl optionally substituted by one or more groups selected from

C_1-C_6alkyl, hydroxy, amino, C_1-C_6alkoxy, or nitro;

R^6 is C_1-C_6alkyl;

R^7 is a cyclopentane ring;

R^8 is phenyl;

$R^9$and R^{10} are independently hydrogen, benzyl, alkenyl, cycloalkyl, C_1-C_6alkyl optionally substituted by hydroxy,

C_1-C_6alkoxy, cyano, di-C_1-C_6alkylamino, phenyl, pyridyl or CO_2R^{11} or R^9 and R^{10} together form a 5- to 7-membered saturated or partially saturated ring optionally containing a further heteroatom and optionally substituted by one or more groups selected from C_1-C_6alkyl (optionally containing an oxygen atom in the chain and optionally substituted by hydroxy), COC_1-C_6alkyl, CO_2R^{11}, $COR^{13}R^{14}$, CHO or piperidine,

R^{11} is hydrogen or C_1-C_6alkyl;

R^{12} is C_1-C_6alkyl; and

R^{13} and R^{14} are independently hydrogen or C_1-C_6alkyl,

and pharmaceutically acceptable salts and solvates thereof.

[0005] In the context of the present specification, unless otherwise indicated, an alkyl substituent or alkyl moiety in a substituent group may be linear or branched and may contain up to 6 carbon atoms, examples of which include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, t-butyl, n-pentyl and n-hexyl.

[0006] Suitably A is phenyl or a 5- or 6-membered heterocyclic ring containing one or two heteroatoms selected from O, N or S; and optionally substituted by $C_{1\text{-}6}$alkyl, halogen, nitro, amino, C_1-C_6alkylamino, CF_3, SO_2Me, $NHSO_2Me$ or cyano. Preferably A is optionally substituted phenyl, more preferably A is phenyl substituted by a nitro group.

[0007] Suitably B is C=O, NH or SO_2. Preferably B is C=O.

[0008] Suitably X is C=O, CH(Me), O or $(CH_2)p$ where p is 0 or 1, Y is O, CH_2, NH or S and Z is C=O or SO_2. Examples of groups formed by X, Y and Z include benzoxazinone and dihydroquinoline. Preferably X is CH_2, Y is O and Z is C=O such that X, Y and Z together form part of a benzoxazinone ring.which can be optionally substituted by methyl.

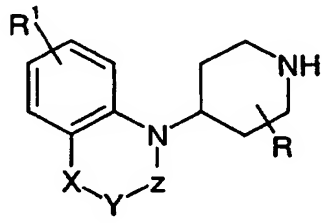
[0009] Suitably R is hydrogen or $C_{1\text{-}6}$alkyl, preferably R is hydrogen.

[0010] Suitably R^1 is hydrogen or halogen, preferably R^1 is hydrogen.

[0011] Suitably R^2 is phenyl optionally substituted by CO_2H, CO_2-C_1-C_6alkyl, $CONH_2$ or R^2 is OH, NHR^3, $NHCH(R^4)(CHR^5)_nR^6$, NH-R^7-R^8, SO_2NHC_1-C_6alkyl, $NHCOC_1$-C_6alkyl, $NHSO_2C_1$-C_6alkyl, morpholine, NR^9R^{10}, piperazine substituted by phenyl, C_1-C_6alkoxyphenyl, pyridyl or fluorophenyl. Preferably R^2 is NR^9R^{10} where one of R^9 or R^{10} is hydrogen and the other is C_1-C_6alkyl such as $CH(CH_3)_2$.

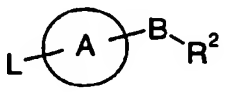
[0012] Particularly preferred compounds of the invention include those exemplified herein both in free base form as well as all pharmaceutically acceptable salts and/or solvates thereof.

[0013] According to the invention there is further provided a process for the preparation of a compound of formula (I) which comprises reaction of a compound of formula (II):



(II)

where R, R^1, X, Y and Z are as defined in formula (I) or a protected derivative thereof, with a compound of formula (III):



(III)

where B and R^2 are as defined in formula (I) or a protected derivative thereof, and L is a leaving group, and optionally thereafter in any order:

- converting one or more functional groups into further functional groups

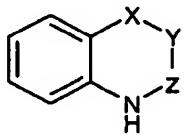
- removing any protecting groups
- forming a pharmaceutically acceptable salt or solvate.

[0014] Examples of suitable leaving groups L include halogen, OMs and OTs. Preferably L is halogen, in particular chloro.

[0015] The reaction of compounds of formula (II) and (III) is preferably carried out in the presence of an organic amine such as a trialkylamine, for example triethylamine. The reaction is preferably carried out in an inert solvent such as NMP, DMF or dioxan preferably at elevated temperature, for example at the reflux temperature of the reaction mixture.

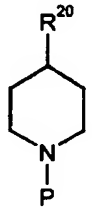
[0016] Compounds of formulae (II) can be prepared as follows:

(a) by reacting a compound of formula (IV):



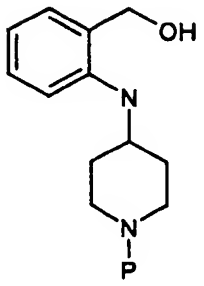
(IV)

in which X, Y and Z are as defined in formula (II) or are protected derivatives thereof, with a compound of formula (V):



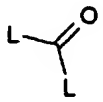
(V)

in which R^{20} is a leaving group or an activated hydroxy group, or
(b) by reacting a compound of formula (VI):



(VI)

in which P a protecting group, with a compound of formula (VII):



(VII)

in which the groups L are leaving groups.

[0017] Compounds of formulae (IV) and (V) can be reacted under Mitsonobu conditions when R^{20} in compound (V) is an activated hydroxy group. For the reaction of compounds (VI) and (VII), examples of suitable leaving L groups include halogen, in particular chloro, or imidazole. Alternatively triphosgene can be used. Suitable protecting groups for compounds (V) and (VI) include t-butoxy carbonyl (Boc).

[0018] Compounds of formula (III), (IV), (V) and (VII) are prepared using literature procedures or are commercially available.

[0019] Functional groups can be converted into further functional groups using procedures known in the art. For example a carboxylic acid group can be converted into an ester or amide using standard chemistry.

[0020] Protecting groups can be added and removed using known reaction conditions. The use of protecting groups is fully described in 'Protective Groups in Organic Chemistry', edited by J W F McOmie, Plenum Press (1973), and 'Protective Groups in Organic Synthesis', 2nd edition, T W Greene & P G M Wutz, Wiley-Interscience (1991).

[0021] Deprotection can be carried out using methods generally known in the art.

[0022] The compounds of formula (I) above may be converted to a pharmaceutically acceptable salt or solvate thereof, preferably an acid addition salt such as a hydrochloride, hydrobromide, phosphate, acetate, fumarate, maleate, tartrate, citrate, oxalate, methanesulphonate or *p*-toluenesulphonate, or an alkali metal salt such as a sodium or potassium salt.

[0023] Certain compounds of formula (I) are capable of existing in stereoisomeric forms. It will be understood that the invention encompasses all geometric and optical isomers of the compounds of formula (I) and mixtures thereof including racemates. Tautomers and mixtures thereof also form an aspect of the present invention.

[0024] The compounds of the present invention are advantageous in that they possess pharmacological activity and have utility as modulators of $P2X_7$ receptor activity.

They are therefore indicated as pharmaceuticals for use in the treatment or prevention of rheumatoid arthritis, osteoarthritis, psoriasis, allergic dermatitis, asthma, hyperresponsiveness of the airway, chronic obstructive pulmonary disease (COPD), bronchitis, septic shock, glomerulonephritis, irritable bowel disease, Crohn's disease, ulcerative colitis, atherosclerosis, growth and metastases of malignant cells, myoblastic leukaemia, diabetes, neurodegenerative disease, Alzheimer's disease, meningitis, osteoporosis, burn injury, ischaemic heart disease, stroke, peripheral vascular disease and varicose veins.

[0025] Accordingly, the present invention provides a compound of formula (I), or a pharmaceutically acceptable salt

or solvate thereof, as hereinbefore defined for use in therapy.

[0026] In another aspect, the invention provides the use of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as hereinbefore defined in the manufacture of a medicament for use in therapy.

[0027] For the above-mentioned therapeutic uses the dosage administered will, of course, vary with the compound employed, the mode of administration, the treatment desired and the disorder indicated.

[0028] The compounds of formula (I) and pharmaceutically acceptable salts and solvates thereof may be used on their own but will generally be administered in the form of a pharmaceutical composition in which the formula (I) compound/salt/solvate (active ingredient) is in association with a pharmaceutically acceptable adjuvant, diluent or carrier. Depending on the mode of administration, the pharmaceutical composition will preferably comprise from 0.05 to 99 %w (per cent by weight), more preferably from 0.10 to 70 %w, of active ingredient, and, from 1 to 99.95 %w, more preferably from 30 to 99.90 %w, of a pharmaceutically acceptable adjuvant, diluent or carrier, all percentages by weight being based on total composition.

[0029] Thus, the present invention also provides a pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as hereinbefore defined in association with a pharmaceutically acceptable adjuvant, diluent or carrier.

[0030] The invention further provides a process for the preparation of a pharmaceutical composition of the invention which comprises mixing a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as hereinbefore defined with a pharmaceutically acceptable adjuvant, diluent or carrier.

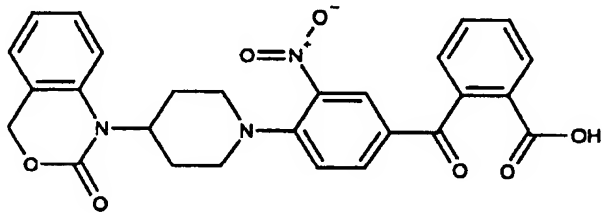
[0031] The pharmaceutical composition of the invention may be administered topically (e.g. to the lung and/or airways or to the skin) in the form of solutions, suspensions, heptafluoroalkane aerosols and dry powder formulations; or systemically, e.g. by oral administration in the form of tablets, capsules, syrups, powders or granules, or by parenteral administration in the form of solutions or suspensions, or by subcutaneous administration or by rectal administration in the form of suppositories or transdermally.

[0032] The present invention will now be further illustrated by reference to the following examples.

Example 1

2-({3-Nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]phenyl}carbonyl)benzoic acid

[0033]



[0034] A solution of 1-piperidin-4-yl-1,4-dihydro-2H-3,1-benzoxazin-2-one hydrochloride (J.Med. Chem. 1998, 2157) (0.8g), 2-(4-chloro-3-nitrobenzoyl)benzoic acid (0.9g) and triethylamine (0.8ml) in N,N-dimethylformamide (5ml) was stirred at room temperature for 72h. The mixture was partitioned between ethyl acetate and dilute hydrochloric acid, the organic layer was evaporated under reduced pressure. Purification was by chromatography eluting with 4% methanol/dichloromethane. The residue was triturated from methanol, yield 0.4g as a solid.

MS: APCI(+ve) 502(M+1)

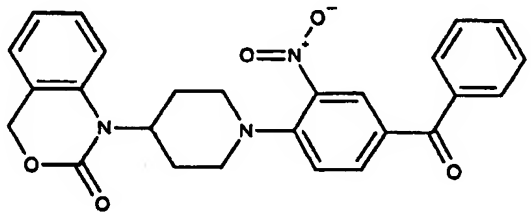
1H NMR: δ (CDC13/DMSO-d6) 8.13-8.05(2H, m), 7.80(1H, d), 7.70-7.57(2H, m), 7.43-7.33(2H, m), 7.23-7.09(4H,m), 5.12(2H, s), 4.20-4.08(1H, m), 3.55(2H, d), 3.21(2H, t), 2.90-2.80(2H, m), 1.97(2H, d)

MP:243-4°C

Example 2

1-{1-[2-Nitro-4-(phenylcarbonyl)phenyl]piperidin-4-yl}-1,4-dihydro-2H-3,1-benzoxazin-2-one

[0035]

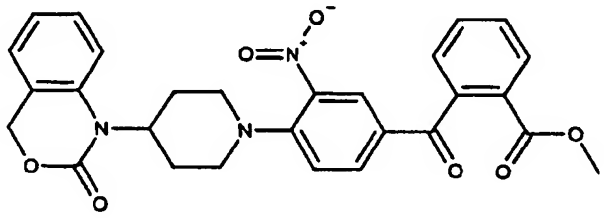


[0036] The title compound was prepared from 1-piperidin-4-yl-1,4-dihydro-2H-3,1-benzoxazin-2-one hydrochloride (0.3g) and 4-chloro-3-nitrobenzophenone (0.29g) using the method of example 1. Yield 0.25g as a solid.
MS: APCI(+ve) 458(M+1) 1H NMR: δ (CDC13/DMSO-d6) 8.28(1H, d), 7.98(1H, dd), 7.78-7.75(2H, m), 7.63-7.60(1H, m), 7.53-7.50(2H,m), 7.38(1H, t), 7.22-7.10(4H, m), 5.11(2H, s), 4.25-4.19(1H, m), 3.61(2H, d), 3.23(2H, t), 2.93-2.84 (2H, m), 1.98(2H, d)
MP:272-3°C

Example 3

Methyl 2-({3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]phenyl}carbonyl)benzoate

[0037]

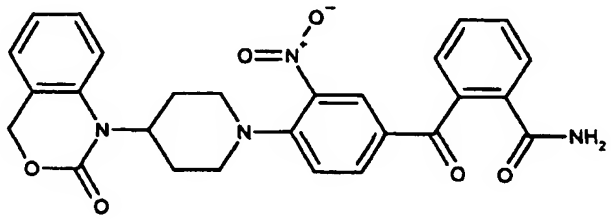


[0038] The product from example 1 was added to methanolic hydrogen chloride and the mixture stirred overnight. The solvent was removed under reduced pressure and the residue purified by chromatography. Yield 0.03g.
MS: APCI(+ve) 516(M+1) 1H NMR: δ ($CDCl_3$) 8.10-8.07(2H, m), 7.91(1H, dd), 7.68-7.57(2H, m), 7.39-7.35(2H, m), 7.19-7.09(4H, m), 5.29(2H, s), 4.22-4.17(1H, m), 3.75(3H, s), 3.57(2H, d), 3.20(2H, t), 2.90-2.81(2H, m), 1.96(2H, d)
MP:177-9°C

Example 4

2-({3-Nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]phenyl}carbonyl)benzamide

[0039]

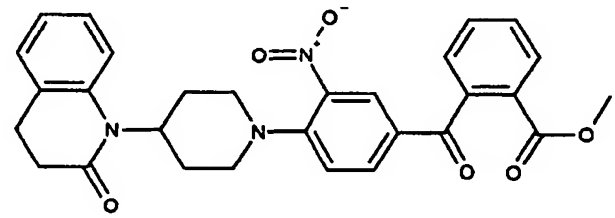


[0040] A solution of the product from example 1 (0.9g) and carbonyldiimidazole (1.1 equiv.) in dichloromethane (4ml) was stirred at room temperature for 1h, poured onto aqueous ammonia and stirred for a further 1h. The mixture was extracted with ethyl acetate, the organics washed with water, dried and evaporated under reduced pressure. Purification was by chromatography eluting with 2.5% methanol/dichloromethane. Yield 0.01g as a solid.
MS: APCI(+ve) 501(M+1)
1H NMR: δ ($CDCl_3$) 8.08(1H, d), 7.64(1H, d), 7.58-7.34(5H, m), 7.20-7.07(4H, m), 7.03(1H, s), 5.08(2H, s), 4.35(1H, s), 4.21-4.13(1H, m), 3.42(2H, d), 3.04(2H, t), 2.86-2.74(2H, m), 1.90(2H, d)
MP:180-2°C

Example 5

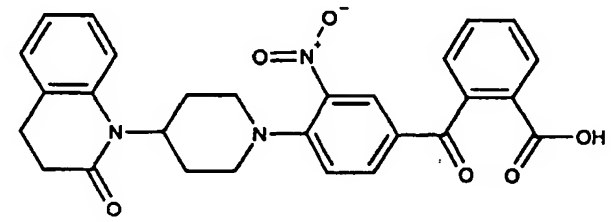
Methyl 2-({3-nitro-4-[4-(2-oxo-3,4-dihydroquinolin-1(2H)-yl)piperidin-1-yl]phenyl}carbonyl)benzoate

[0041]



(i) 2-({3-Nitro-4-[4-(2-oxo-3,4-dihydroquinolin-1(2H)-yl)piperidin-1-yl]phenyl}carbonyl)benzoic acid

[0042]



[0043] The product was prepared from 1-piperidin-4-yl-3,4-dihydroquinolin-2(1H)-one (Chem. Pharm. Bull. (1996), 44(4), 725-33) (0.45g) and 2-(4-chloro-3-nitrobenzoyl)benzoic acid (0.6g) using the method of example 1. Used crude.

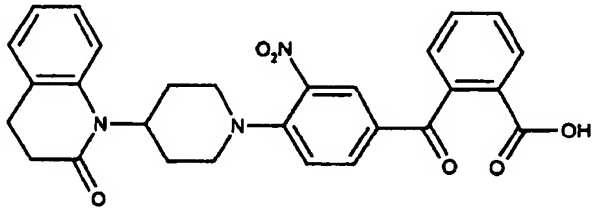
(ii) Methyl 2-({3-nitro-4-[4-(2-oxo-3,4-dihydroquinolin-1(2H)-yl)piperidin-1-yl]phenyl}carbonyl)benzoate

[0044] The title compound was prepared from the product from step (i) (0.2g) which was added to methanolic hydrogen chloride and stirred at room temperature overnight. The solvent was removed under reduced pressure and the residue partitioned between ethyl acetate and aqueous sodium hydrogencarbonate solution. The organics were separated, dried and evaporated under reduced pressure. Purification was by chromatography to yield 0.18g of a solid.
MS: APCI(+ve) 514(M+1)
1H NMR: δ ($CDCl_3$) 8.09-8.07(2H, m), 7.92(1H, dd), 7.68-7.56(2H, m), 7.37(1H, d), 7.26-7.13(4H, m), 7.03(1H, t), 4.50-4.46(1H, m), 3.74(3H, s), 3.53(2H, d), 3.18(2H, t), 2.86-2.75(4H, m), 2.61-2.57(2H, m), 1.84(2H, d)
MP:112-3°C

Example 6

2-({3-Nitro-4-[4-(2-oxo-3,4-dihydroquinolin-1(2H)-yl)piperidin-1-yl]phenyl}carbonyl)benzoic acid

[0045]

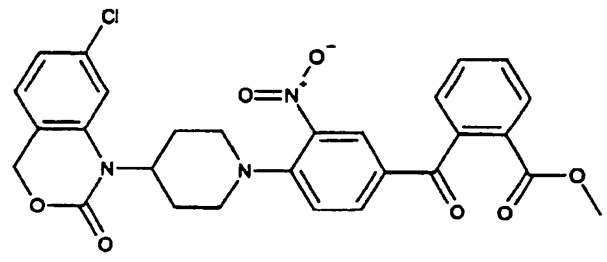


[0046] Lithium hydroxide hydrate (3 equiv.) was added to a mixture of the product from example 5 step (ii) (0.15g) in methanol/water (5.5ml, 10:1) and stirred overnight at room temperature. The solvent was removed under reduced pressure, the residue dissolved in water and neutralised with dilute hydrochloric acid. The mixture was extracted with ethyl acetate, dried and evaporated under reduced pressure. The residue was triturated with ether and the solid collected. Yield 0.06g.
MS: APCI(+ve) 500(M+1)
1H NMR: δ ($CDCl_3$) 8.11(2H, m), 7.86(1H, dd), 7.71(1H, m), 7.59(1H, m), 7.38(1H, dd), 7.18(4H, m), 7.01(1H, m), 4.48 (1H, m), 3.51(2H, m), 3.16(2H, m), 2.83(4H, m), 2.27(2H, m), 1.84(2H, m)
MP:201-203°C

Example 7

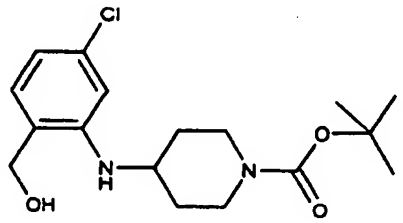
Methyl 2-({4-[4-(7-chloro-2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]-3-nitrophenyl}carbonyl)benzoate

[0047]



(i) 1,1-Dimethylethyl 4-{[5-chloro-2-(hydroxymethyl)phenyl]amino}piperidine-1-carboxylate

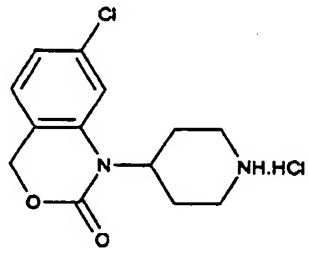
[0048]



[0049] N-tert-Butoxycarbonyl-4-piperidone (5.8g), 2-amino-5-chlorobenzyl alcohol (5.02g) and acetic acid (4ml) in toluene (200ml) were heated under reflux using a Dean-Stark trap for 1.5h. The solvent was evaporated under reduced pressure to ~100ml, tetrahydrofuran (100ml) added followed by sodium cyanoborohydride (6.3g). Acetic acid (3ml) was added dropwise to this mixture which was stirred at room temperature for 96h. The solvents were removed under reduced pressure and the residue partitioned between ethyl acetate and aqueous sodium hydrogencarbonate solution. The organics were dried, evaporated under reduced pressure and the residue triturated with dichloromethane/isohexane. Yield 7.5g.
MS: APCI(+ve) 500(M+1)

(ii) 7-Chloro-1-piperidin-4-yl-1,4-dihydro-2H-3,1-benzoxazin-2-one hydrochloride

[0050]



[0051] Triphosgene (1.6g) was added to a stirred solution of the product from step (i) (5g), N,N-diisopropylethylamine (5.2ml) in tetrahydrofuran (50ml) at 0°C. The mixture was stirred at room temperature for 16h, the precipitate filtered and the filtrate evaporated under reduced pressure. Purification was by chromatography eluting with 20% ethyl acetate/toluene. The product was dissolved in dichloromethane then a solution of hydrogen chloride in 1,4-dioxane added. After 2h the solvent was removed under reduced pressure to yield a solid. Used directly.

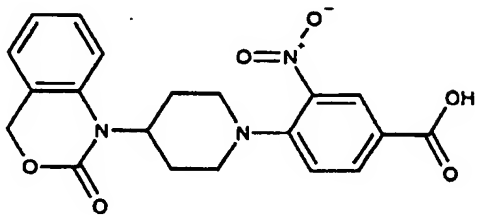
(iii) Methyl 2-({4-[4-(7-chloro-2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]-3-nitrophenyl}carbonyl) benzoate

[0052] Methyl 2-[(4-chloro-3-nitrophenyl)carbonyl]benzoate (0.5g), the product from step (ii) (0.47g) and triethylamine (0.5ml) in N,N-dimethylformamide (2.5ml) were heated at 60°C overnight. The mixture was evaporated under reduced pressure and the residue purified by chromatography eluting with 25% ethyl acetate/toluene. Yield 0.7g of a solid.
MS: APCI(+ve) 550(M+1)
1H NMR: δ (DMSO-d6) 8.00-7.97(2H, m), 7.80-7.72(2H, m), 7.70-7.65(1H, m), 7.46(1H, d), 7.40-7.30(4H, m), 5.12 (2H, s), 4.20-4.10(1H, m), 3.64(3H, s), 3.49(2H, br d), 3.26(2H, br t), 2.70-2.60(2H, m), 1.97-1.91(2H, m)
MP:90-2°C

Examples 8-114

(I) 3-Nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzoic acid

[0053]



[0054] A solution of 1-piperidin-4-yl-1,4-dihydro-2H-3,1-benzoxazin-2-one hydrochloride (1.0g), 1,1-dimethylethyl 4-chloro-3-nitrobenzoate (0.95g) and triethylamine (0.8g) in N,N-dimethylformamide (10ml) was stirred at room temperature overnight. The mixture was partitioned between ethyl acetate and water. The organic layer was dried, and evaporated under reduced pressure. Purification was by chromatography eluting with 1:2 ethyl acetate-isohexane. The residue was dissolved in formic acid (5ml) stirred overnight at room temperature, heated at 55°C for 2h, then evaporated under reduced pressure. The residue was triturated with ether, yield 0.85g as a solid.
MS: APCI(+ve) 398(M+1)

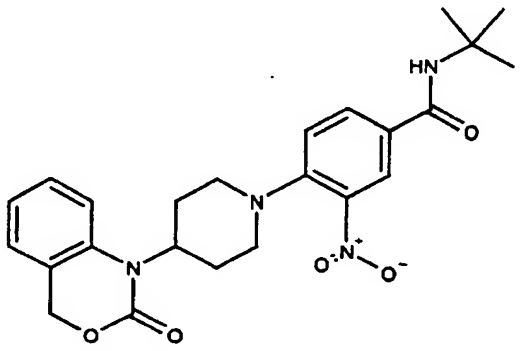
(II) Examples 8-114

[0055] Carbonyldiimidazole (0.2g) was added to a solution of the product from step (i) (0.4g) in N,N-dimethylformamide (25ml) and stirred at room temperature for 2.5h. The activated acid (0.1ml) the appropriate amine (5 equivalents) and triethylamine (5 equivalents) in 1-methyl-2-pyrrolidinone (0.1ml) were left at room temperature for 24h. The reaction mixture was evaporated to dryness and the residue dissolved in dimethylsulphoxide (0.4ml).

Example 8

N-(1,1-Dimethylethyl)-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide

[0056]

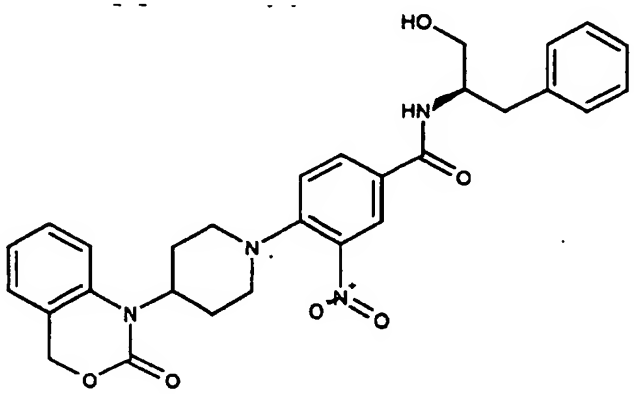


MS: APCI(+ve) 453(M+1)

Example 9

N-[(1R)-2-Hydroxy-1-(phenylmethyl)ethyl]-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl] benzamide

[0057]

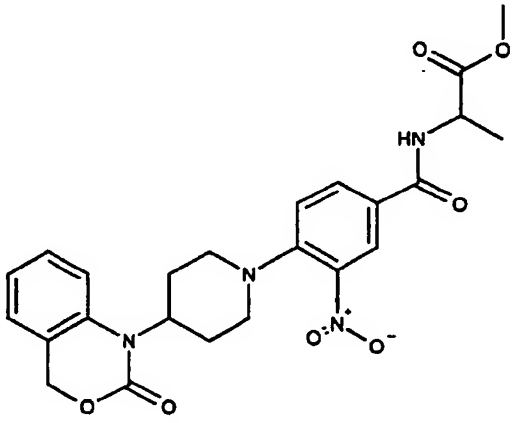


MS: APCI(+ve) 531(M+1)

Example 10

Methyl 2-[({3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]phenyl}carbonyl)amino]propanoate

[0058]

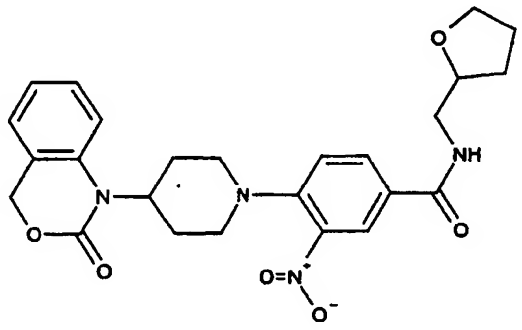


MS: APCI(+ve) 483(M+1)

Example 11

3-Nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]-N-(tetrahydrofuran-2-ylmethyl)benzamide

[0059]

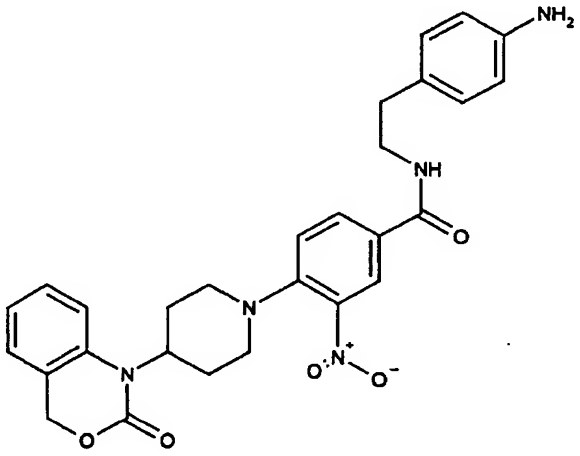


MS: APCI(+ve) 481(M+1)

Example 12

N-[2-(4-Aminophenyl)ethyl]-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide

[0060]

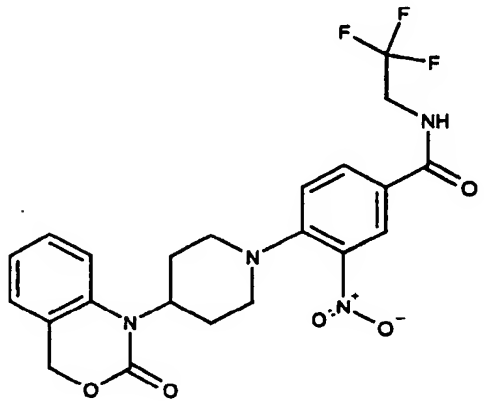


MS: APCI(+ve) 516(M+1)

Example 13

3-Nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]-N-(2,2,2-trifluoroethyl)benzamide

[0061]

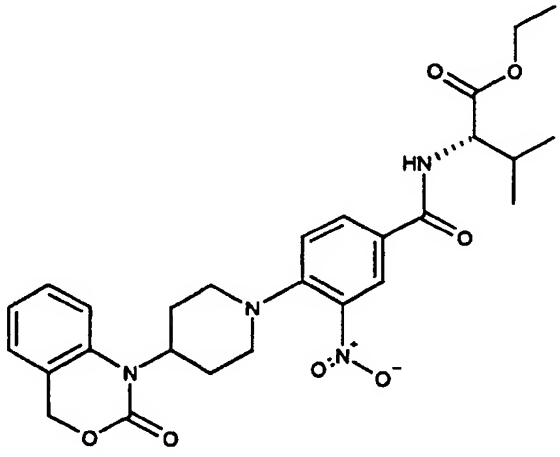


MS: APCI(+ve) 479(M+1)

Example 14

Ethyl (2S)-3-methyl-2-[({3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]phenyl}carbonyl)amino] butanoate

[0062]

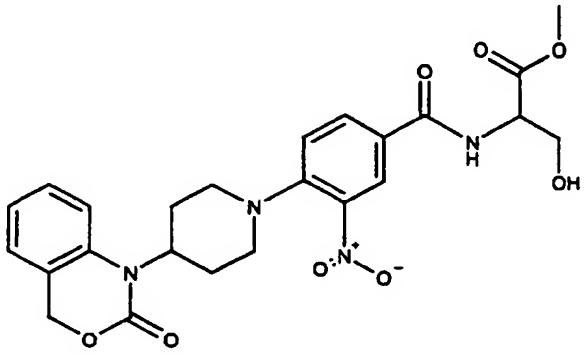


MS: APCI(+ve) 525(M+1)

Example 15

Methyl 3-hydroxy-2-[({3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]phenyl}carbonyl)amino] propanoate

[0063]

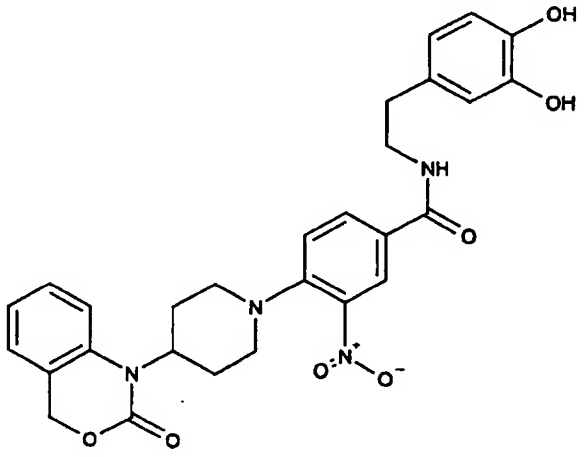


MS: APCI(+ve) 499(M+1)

Example 16

N-[2-(3,4-Dihydroxyphenyl)ethyl]-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide

[0064]

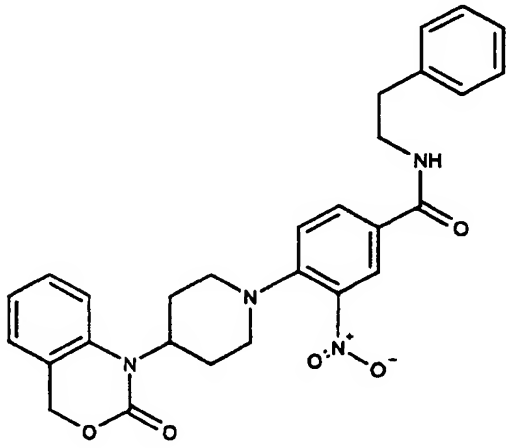


MS: APCI(+ve) 533(M+1)

Example 17

3-Nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]-N-(2-phenylethyl)benzamide

[0065]

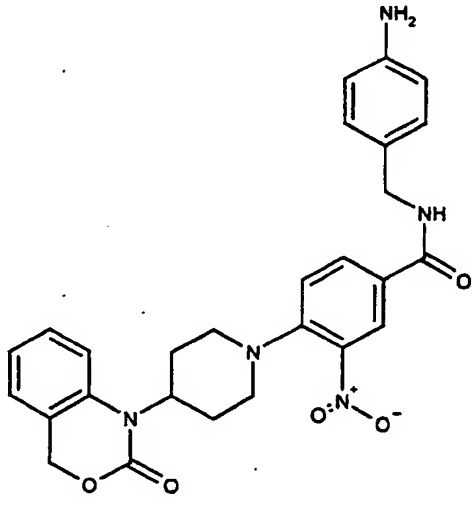


MS: APCI(+ve) 501(M+1)

Example 18

N-[(4-Aminophenyl)methyl]-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide

[0066]

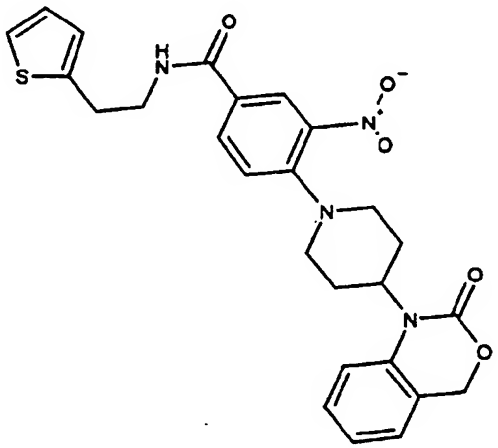


MS: APCI(+ve) 502(M+1)

Example 19

3-Nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]-N-(2-thien-2-ylethyl)benzamide

[0067]

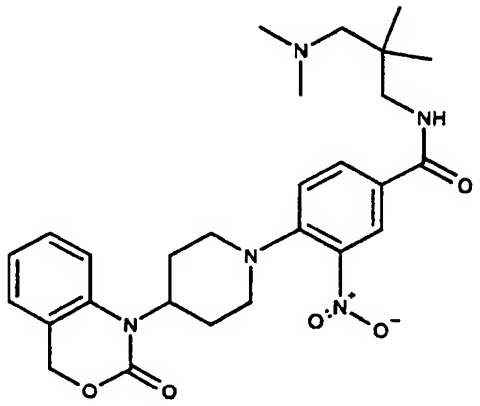


MS: APCI(+ve) 507(M+1)

Example 20

N-[3-(Dimethylamino)-2,2-dimethylpropyl]-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl] benzamide

[0068]

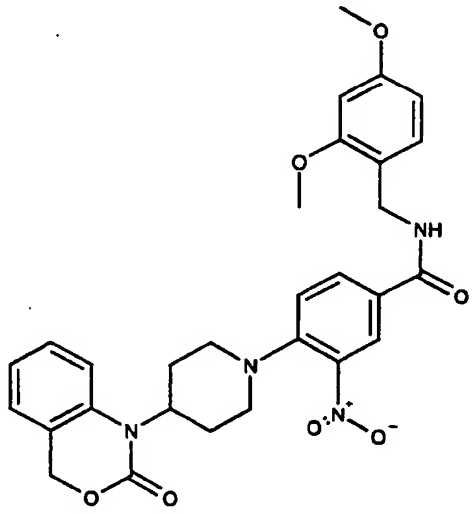


MS: APCI(+ve) 510(M+1)

Example 21

N-{[2,4-Bis(methyloxy)phenyl]methyl}-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl] benzamide

[0069]

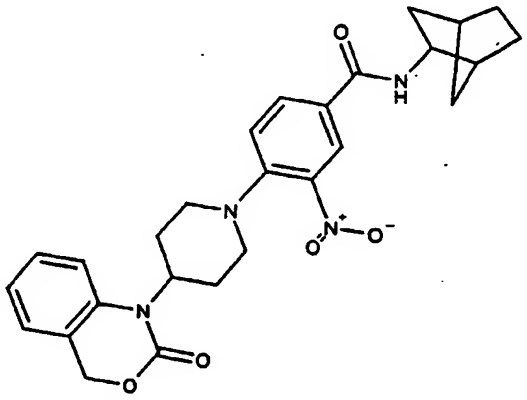


MS: APCI(+ve) 547(M+1)

Example 22

N-Bicyclo[2.2.1]hept-2-yl-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide

[0070]

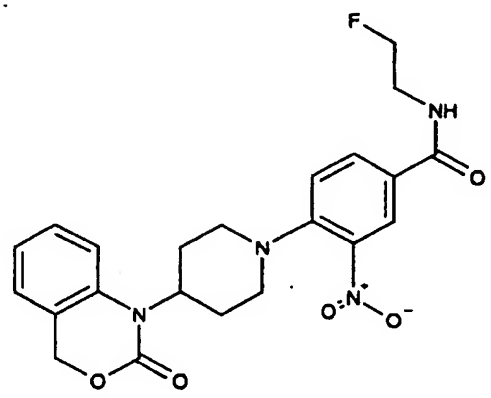


MS: APCI(+ve) 491(M+1)

Example 23

N-(2-Fluoroethyl)-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide

[0071]

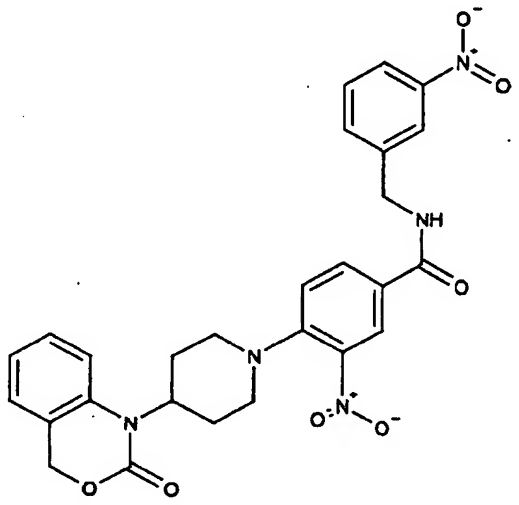


MS: APCI(+ve) 443 (M+1)

Example 24

3-Nitro-N-[(3-nitrophenyl)methyl]-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide

[0072]

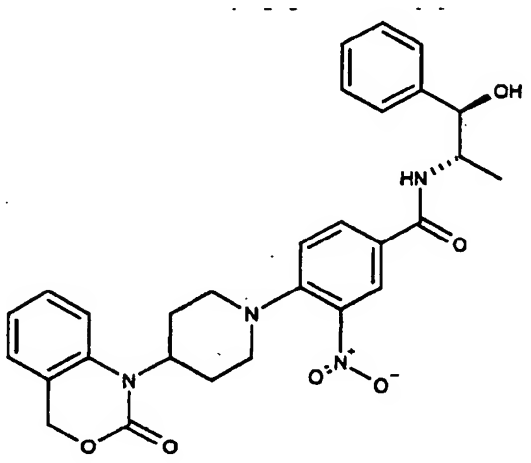


MS: APCI(+ve) 532(M+1)

Example 25

N-[(1 S,2R)-2-Hydroxy-1-methyl-2-phenylethyl]-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl] benzamide

[0073]

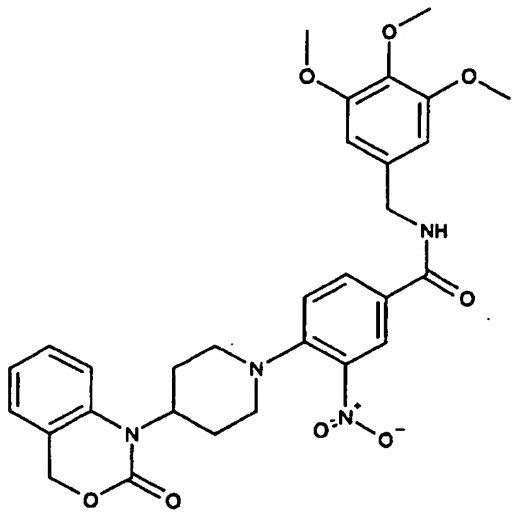


MS: APCI(+ve) 531(M+1)

Example 26

3-Nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]-N-{[3,4,5-tris(methyloxy)phenyl]methyl} benzamide

[0074]

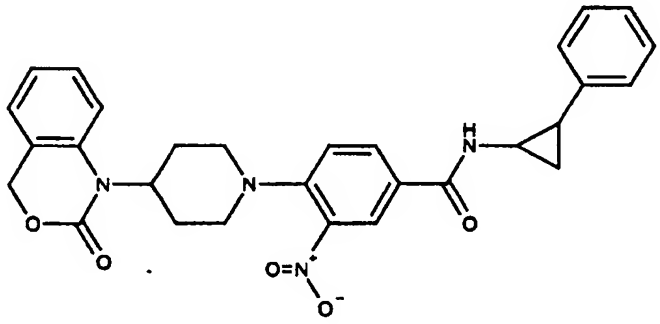


MS: APCI(+ve) 577(M+1)

Example 27

3-Nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]-N-(2-phenylcyclopropyl)benzamide

[0075]

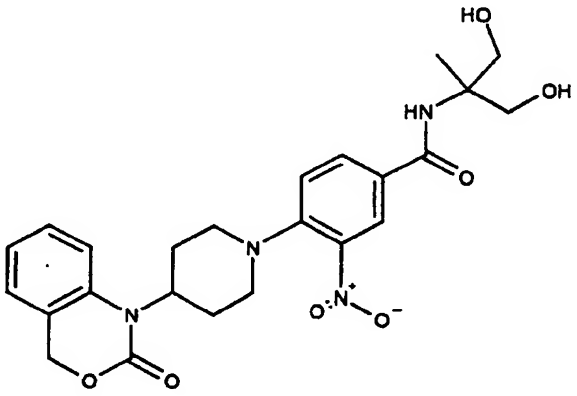


MS: APCI(+ve) 513(M+1)

Example 28

N-[2-Hydroxy-1-(hydroxymethyl)-1-methylethyl]-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl] benzamide

[0076]

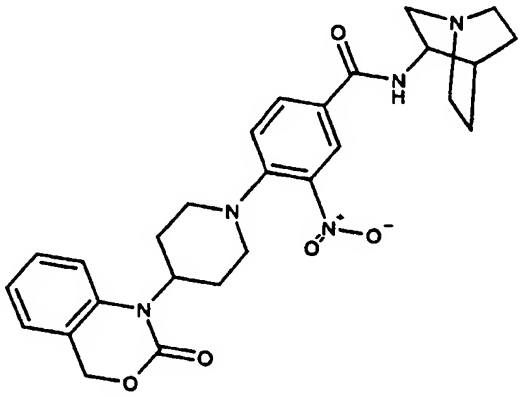


MS: APCI(+ve) 485(M+1)

Example 29

N-(1-Azabicyclo[2.2.2]oct-3-yl)-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide

[0077]

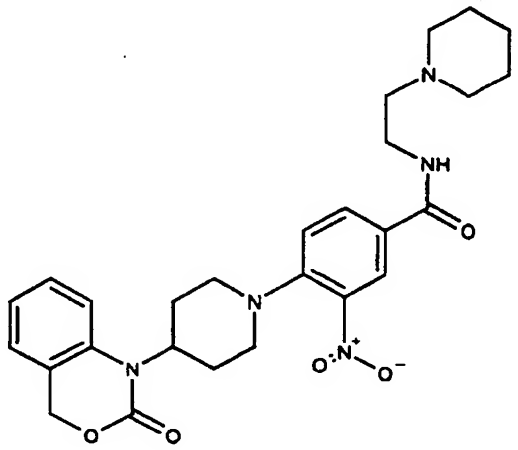


MS: APCI(+ve) 506(M+1)

Example 30

3-Nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]-N-(2-piperidin-1-ylethyl)benzamide

[0078]

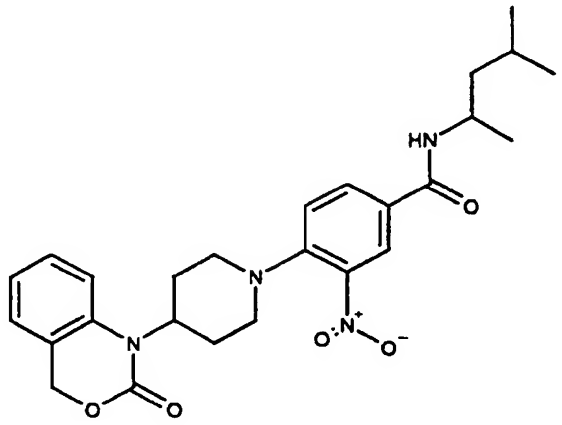


MS: APCI(+ve) 508(M+1)

Example 31

N-(1,3-Dimethylbutyl)-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide

[0079]

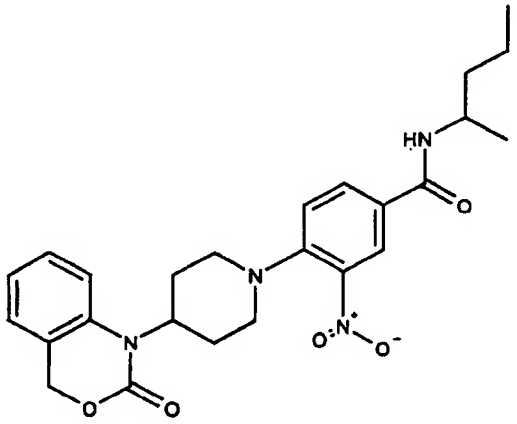


MS: APCI(+ve) 481(M+1)

Example 32

N-(1-Methylbutyl)-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide

[0080]

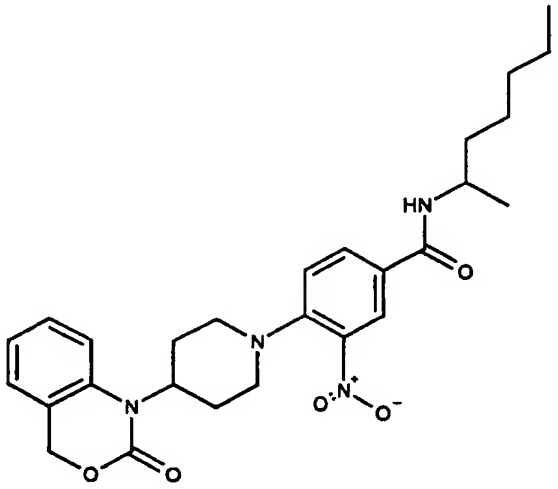


MS: APCI(+ve) 467(M+1)

Example 33

N-(1-Methylhexyl)-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide

[0081]

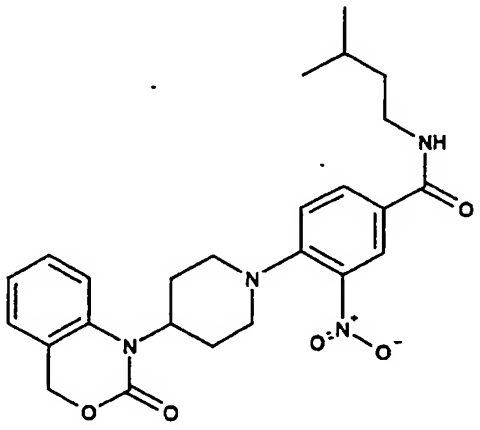


MS: APCI(+ve) 495(M+1)

Example 34

N-(3-Methylbutyl)-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide

[0082]

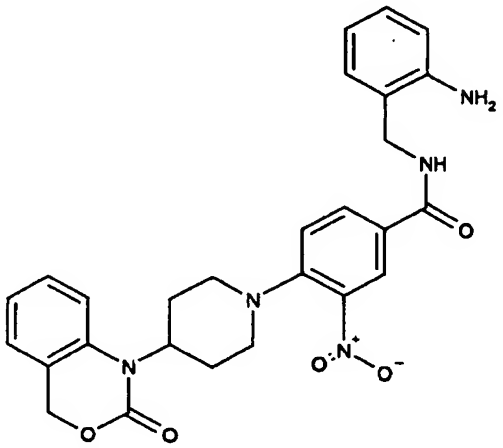


MS: APCI(+ve) 467(M+1)

Example 35

N-[(2-Aminophenyl)methyl]-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide

[0083]

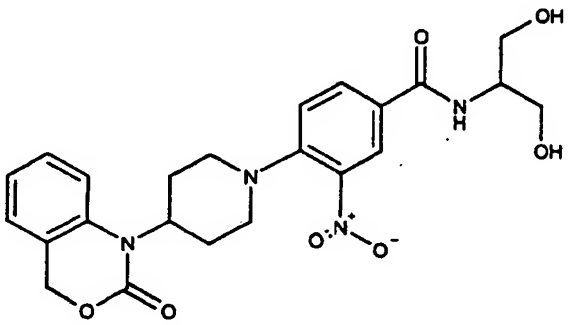


MS: APCI(+ve) 502(M+1)

Example 36

N-[2-Hydroxy-1-(hydroxymethyl)ethyl]-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-l-yl] benzamide

[0084]

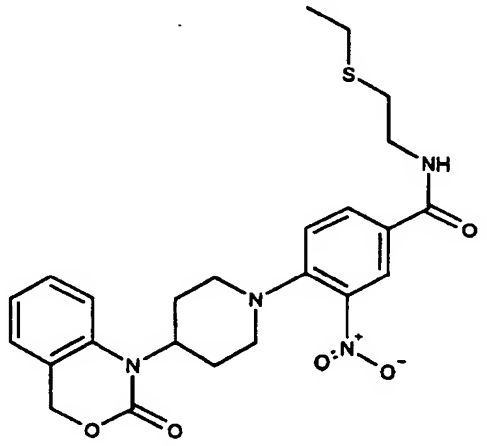


MS: APCI(+ve) 471(M+1)

Example 37

N-[2-(Ethylthio)ethyl]-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide

[0085]

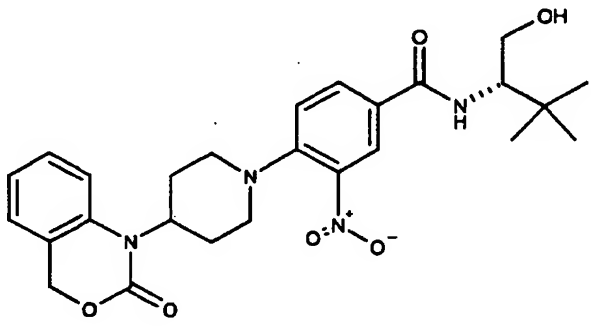


MS: APCI(+ve) 485(M+1)

Example 38

N-[(1S)-1-(Hydroxymethyl)-2,2-dimethylpropyl]-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl] benzamide

[0086]

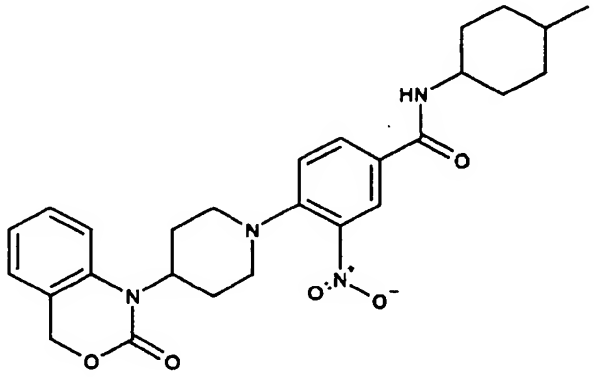


MS: APCI(+ve) 497(M+1)

Example 39

N-(4-Methylcyclohexyl)-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide

[0087]

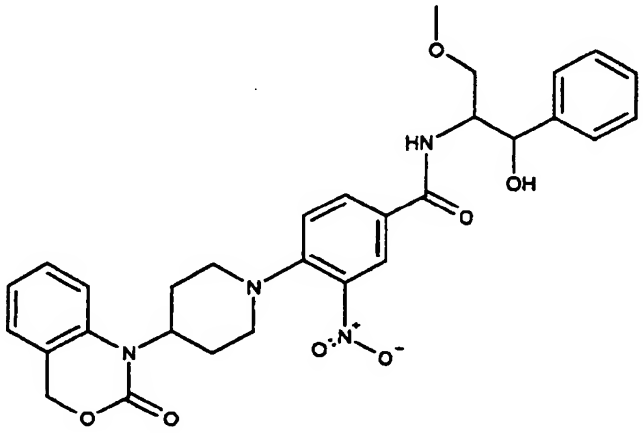


MS: APCI(+ve) 493(M+1)

Example 40

N-{2-Hydroxy-1-[(methyloxy)methyl]-2-phenylethyl}-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide

[0088]

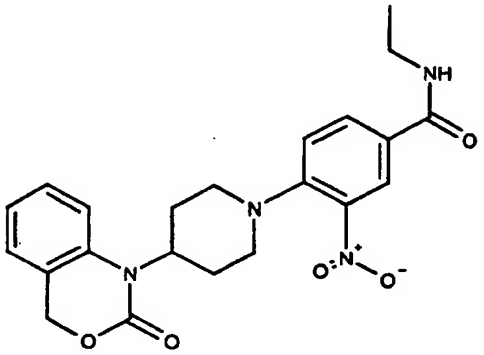


MS: APCI(+ve) 561(M+1)

Example 41

N-Ethyl-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide

[0089]

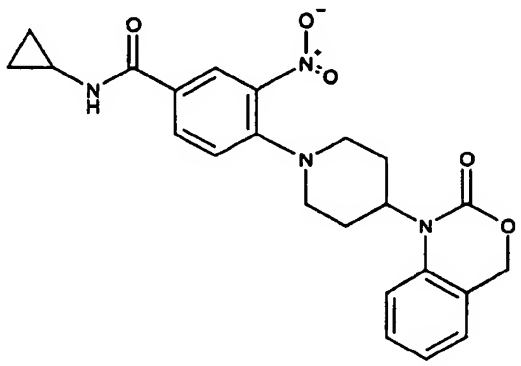


MS: APCI(+ve) 425(M+1)

Example 42

N-Cyclopropyl-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide

[0090]

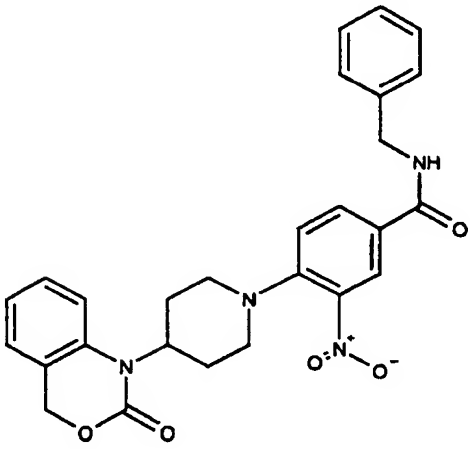


MS: APCI(+ve) 437(M+1)

Example 43

3-Nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]-N-(phenylmethyl)benzamide

[0091]

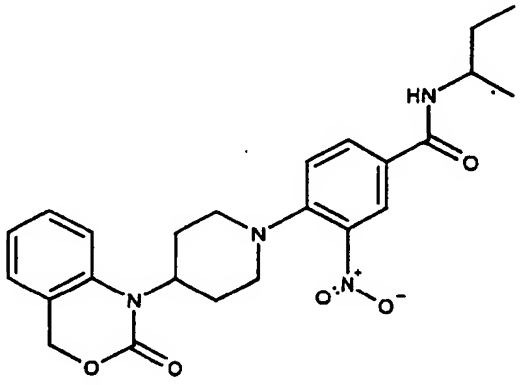


MS: APCI(+ve) 487(M+1)

Example 44

N-(1-Methylpropyl)-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide

[0092]

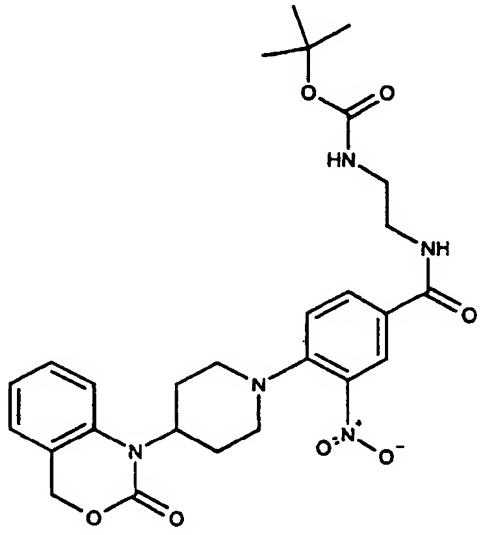


MS: APCI(+ve) 453(M+1)

Example 45

1,1-Dimethylethyl 2-[({3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]phenyl} carbonyl)amino] ethylcarbamate

[0093]

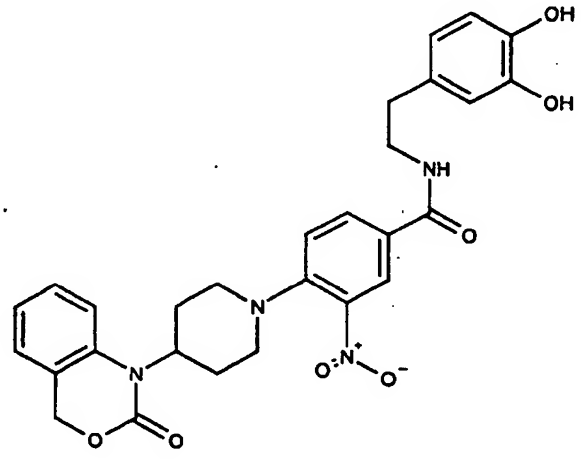


MS: APCI(+ve) 440(M+1-Boc)

Example 46

N-[2-(3,4-Dihydroxyphenyl)ethyl]-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide

[0094]

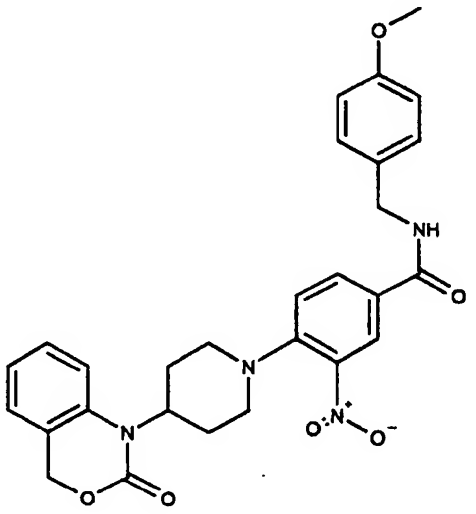


MS: APCI(+ve) 533(M+1)

Example 47

N-{[4-(Methyloxy)phenyl]methyl}-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide

[0095]

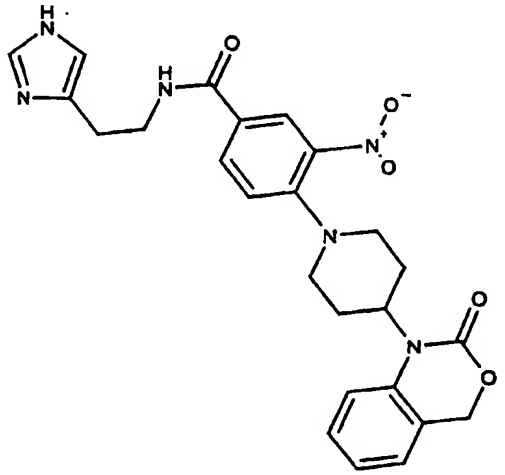


MS: APCI(+ve) 517(M+1)

Example 48

N-[2-(1H-Imidazol-4-yl)ethyl]-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide

[0096]

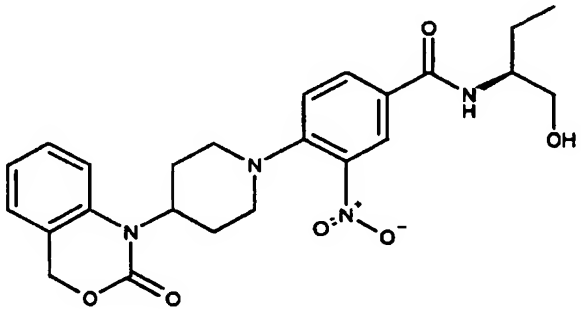


MS: APCI(+ve) 491(M+1)

Example 49

N-[(1S)-1-(Hydroxymethyl)propyl]-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide

[0097]

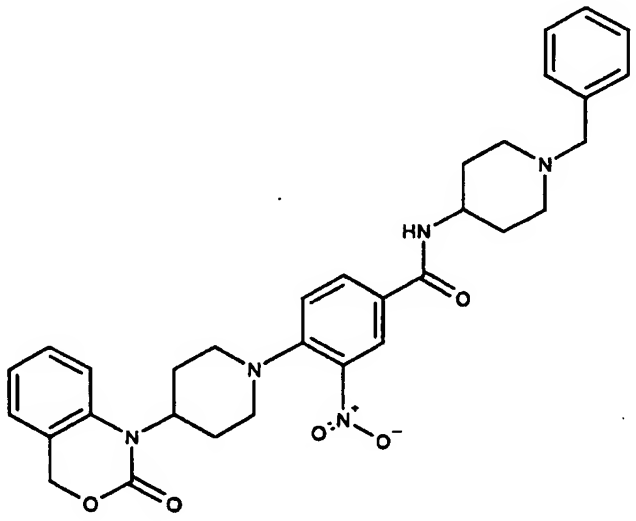


MS: APCI(+ve) 469(M+1)

Example 50

3-Nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]-N-[1-(phenylmethyl)piperidin-4-yl]benzamide

[0098]

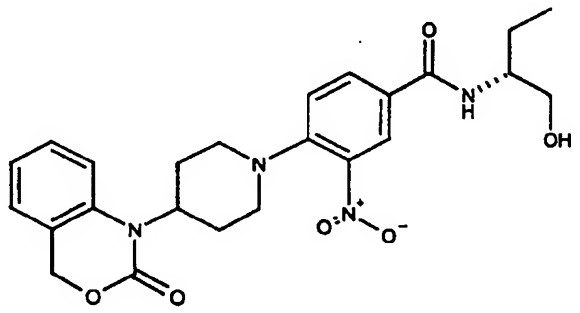


MS: APCI(+ve) 570(M+1)

Example 51

N-[(IR)-1-(Hydroxymethyl)propyl]-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide

[0099]

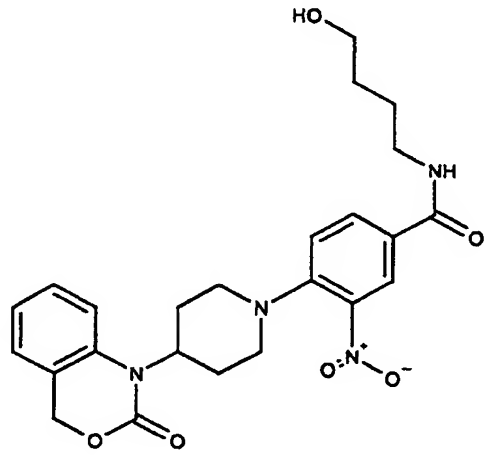


MS: APCI(+ve) 469(M+1)

Example 52

N-(4-Hydroxybutyl)-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide

[0100]

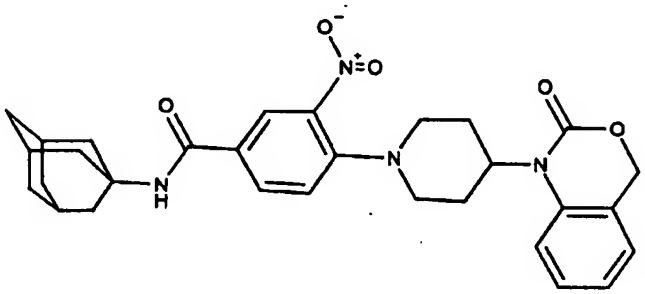


MS: APCI(+ve) 469(M+1)

Example 53

3-Nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]-N-tricyclo[3.3.1.1~3,7~]dec-1-ylbenzamide

[0101]

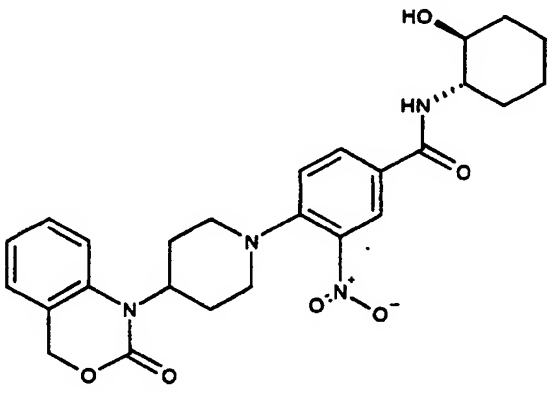


MS: APCI(+ve) 531(M+1)

Example 54

N-[(1S,2S)-2-Hydroxycyclohexyl]-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide

[0102]

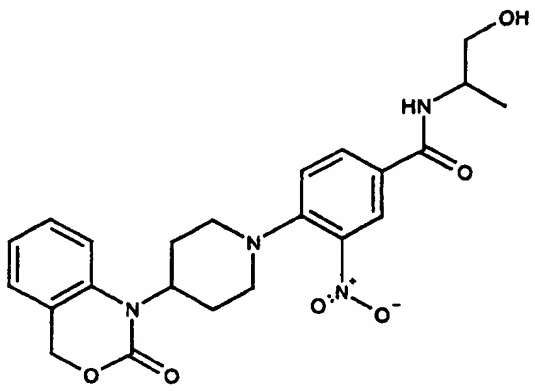


MS: APCI(+ve) 495(M+1)

Example 55

N-(2-Hydroxy-1-methylethyl)-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide

[0103]

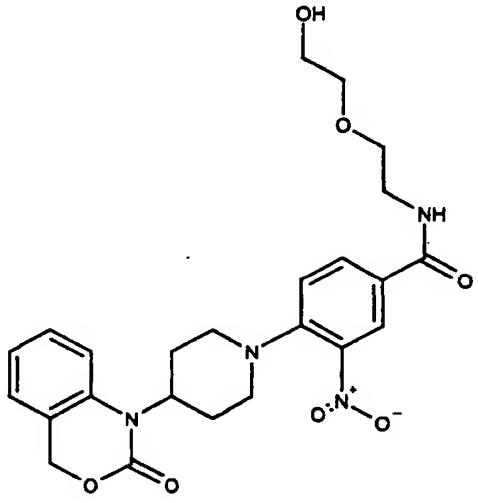


MS: APCI(+ve) 455(M+1)

Example 56

N-{2-[(2-Hydroxyethyl)oxy]ethyl}-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide

[0104]

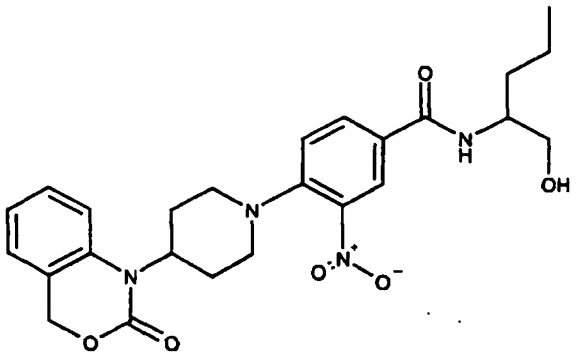


MS: APCI(+ve) 485(M+1)

Example 57

N-[1-(Hydroxymethyl)butyl]-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide

[0105]

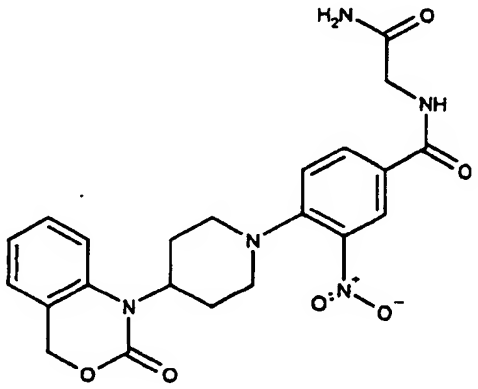


MS: APCI(+ve) 483(M+1)

Example 58

N-(2-Amino-2-oxoethyl)-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide

[0106]

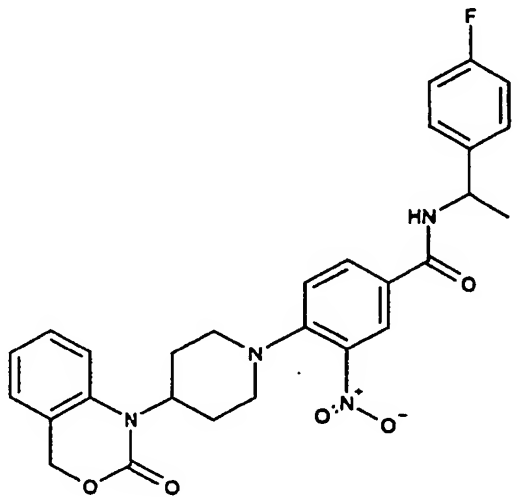


MS: APCI(+ve) 454(M+1)

Example 59

N-[1-(4-Fluorophenyl)ethyl]-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide

[0107]

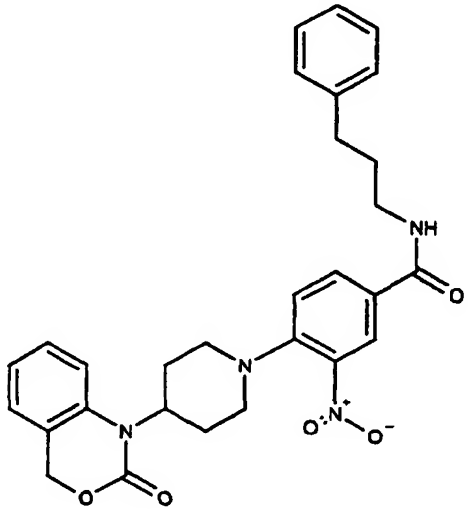


MS: APCI(+ve) 519(M+1)

Example 60

3-Nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]-N-(3-phenylpropyl)benzamide

[0108]

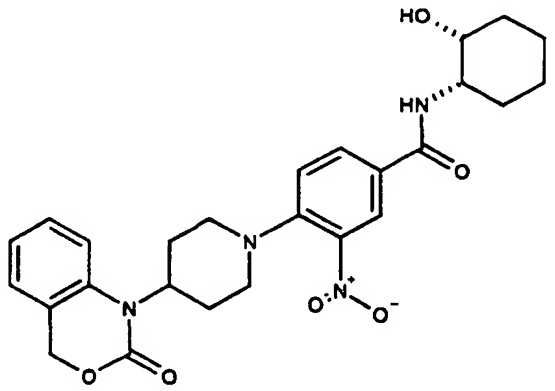


MS: APCI(+ve) 515(M+1)

Example 61

N-[(1S,2R)-2-Hydroxycyclohexyl]-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide

[0109]

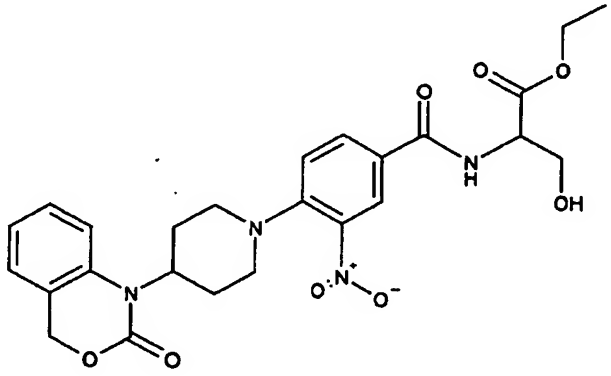


MS: APCI(+ve) 495(M+1)

Example 62

Ethyl 3-hydroxy-2-[({3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]phenyl}carbonyl)amino] propanoate

[0110]

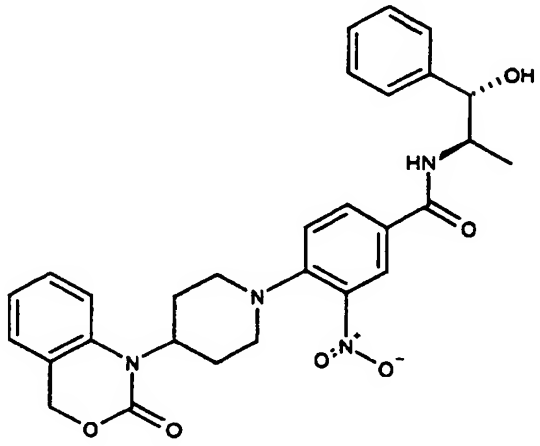


MS: APCI(+ve) 513(M+1)

Example 63

N-[(1R,2S)-2-Hydroxy-1-methyl-2-phenylethyl]-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl] benzamide

[0111]

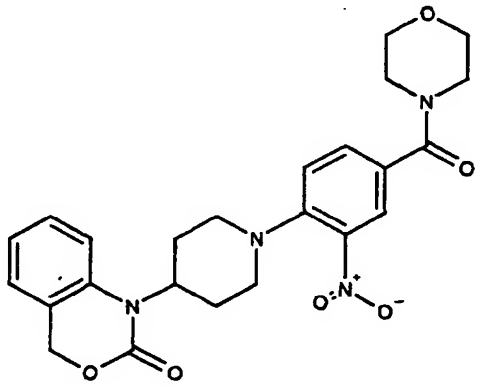


MS: APCI(+ve) 531(M+1)

Example 64

1-{1-[4-(Morpholin-4-ylcarbonyl)-2-nitrophenyl]piperidin-4-yl}-1,4-dihydro-2H-3,1-benzoxazin-2-one

[0112]

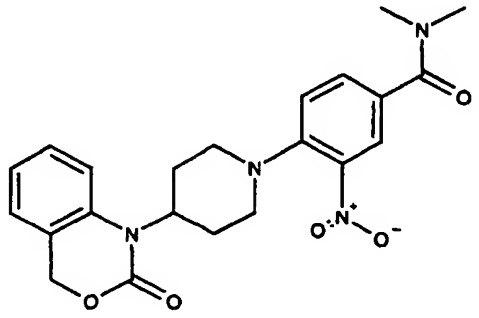


MS: APCI(+ve) 467(M+1)

Example 65

N,N-Dimethyl-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide

[0113]

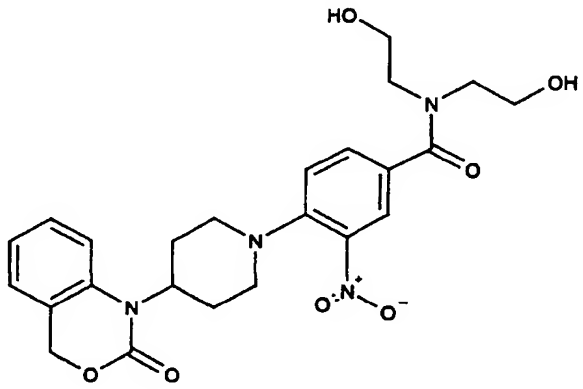


MS: APCI(+ve) 425(M+1)

Example 66

N,N-Bis(2-hydroxyethyl)-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide

[0114]

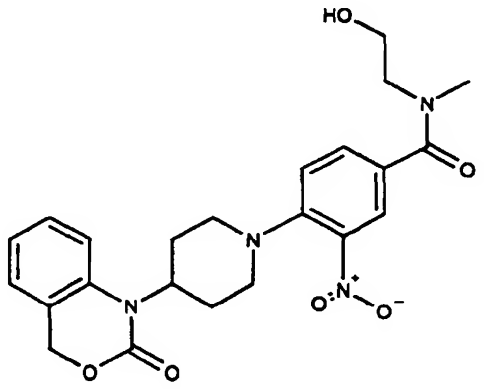


MS: APCI(+ve) 485 (M+1)

Example 67

N-(2-Hydroxyethyl)-N-methyl-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide

[0115]

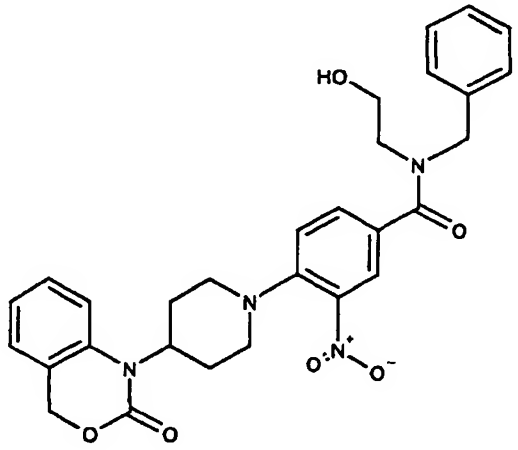


MS: APCI(+ve) 455(M+1)

Example 68

N-(2-Hydroxyethyl)-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]-N-(phenylmethyl)benzamide

[0116]

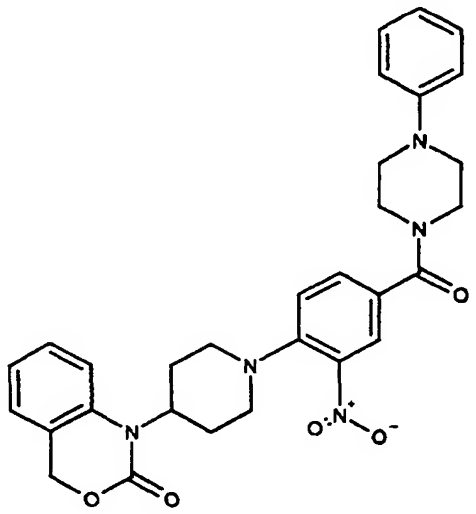


MS: APCI(+ve) 531 (M+1)

Example 69

1-(1-{2-Nitro-4-[(4-phenylpiperazin-1-yl)carbonyl]phenyl}piperidin-4-yl)-1,4-dihydro-2H-3,1-benzoxazin-2-one

[0117]

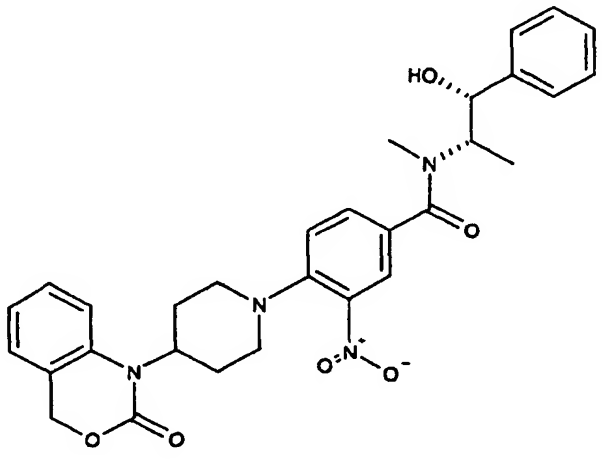


MS: APCI(+ve) 542(M+1)

Example 70

N-[(1S,2R)-2-hydroxy-1-methyl-2-phenylethyl]-N-methyl-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl) piperidin-1-yl]benzamide

[0118]

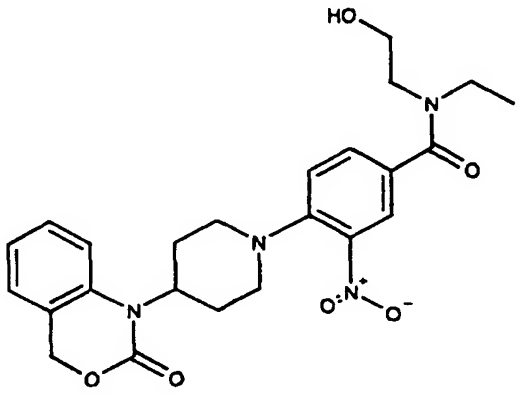


MS: APCI(+ve) 545(M+1)

Example 71

N-Ethyl-N-(2-hydroxyethyl)-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide

[0119]

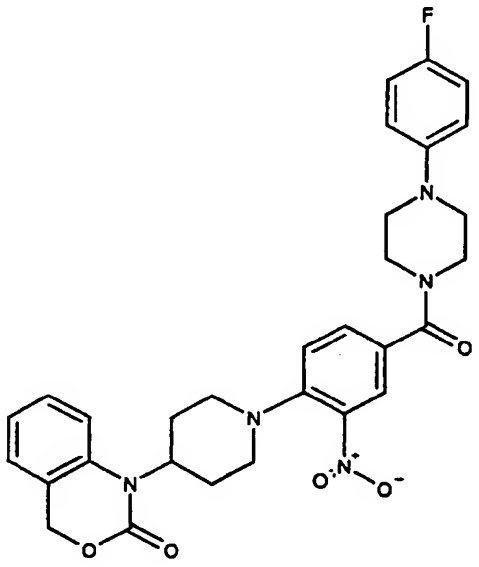


MS: APCI(+ve) 469(M+1)

Example 72

1-[1-(4-{[4-(4-Fluorophenyl)piperazin-1-yl]carbonyl}-2-nitrophenyl)piperidin-4-yl]-1,4-dihydro-2H-3,1-benzoxazin-2-one

[0120]

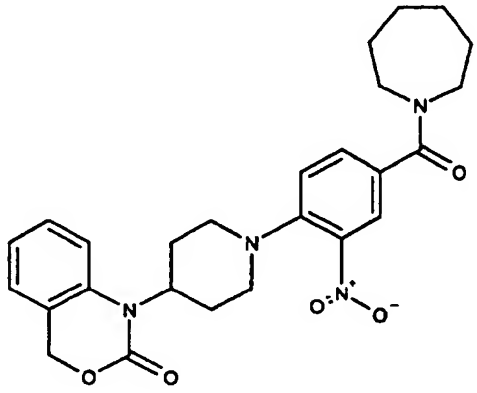


MS: APCI(+ve) 560(M+1)

Example 73

1-{1-[4-(Azepan-1-ylcarbonyl)-2-nitrophenyl]piperidin-4-yl}-1,4-dihydro-2H-3,1-benzoxazin-2-one

[0121]

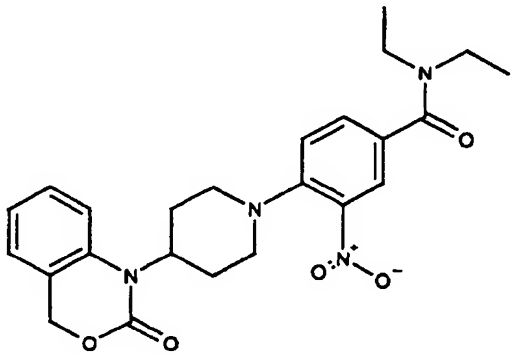


MS: APCI(+ve) 479(M+1)

Example 74

N,N-Diethyl-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide

[0122]

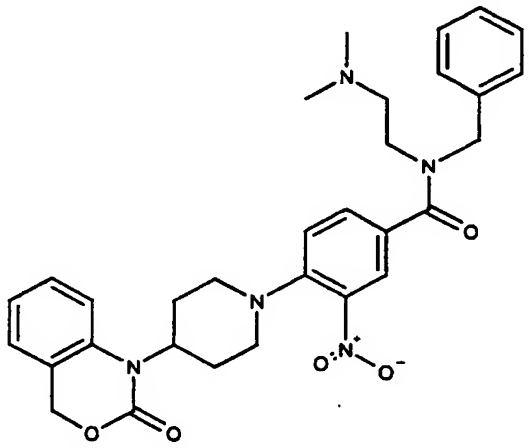


MS: APCI(+ve) 453(M+1)

Example 75

N-[2-(Dimethylamino)ethyl]-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]-N-(phenylmethyl) benzamide

[0123]

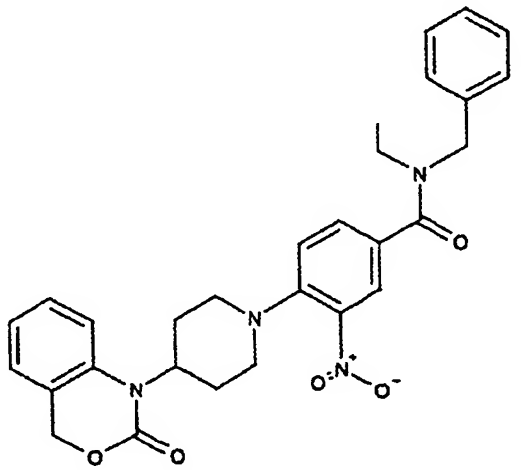


MS: APCI(+ve) 558(M+1)

Example 76

N-Ethyl-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]-N-(phenylmethyl)benzamide

[0124]

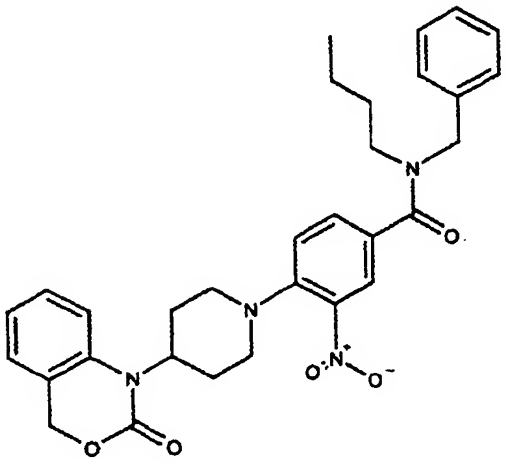


MS: APCI(+ve) 515(M+1)

Example 77

N-Butyl-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]-N-(phenylmethyl)benzamide

[0125]

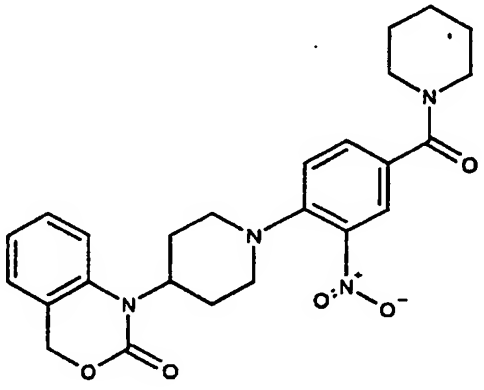


MS: APCI(+ve) 543(M+1)

Example 78

1-{1-[2-Nitro-4-(piperidin-1-ylcarbonyl)phenyl]piperidin-4-yl}-1,4-dihydro-2H-3,1-benzoxazin-2-one

[0126]

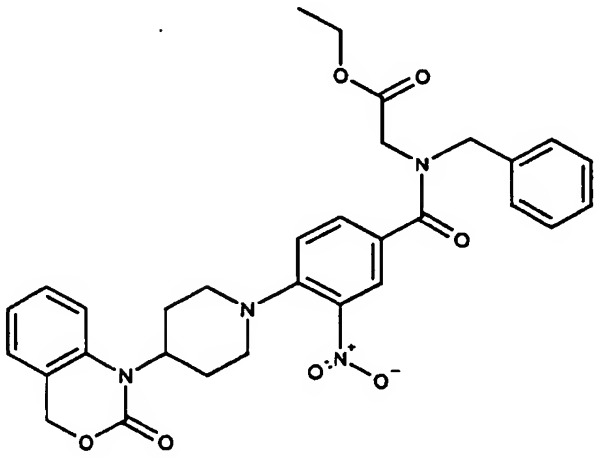


MS: APCI(+ve) 465(M+1)

Example 79

Ethyl [({3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]phenyl}carbonyl)(phenylmethyl)amino] acetate

[0127]

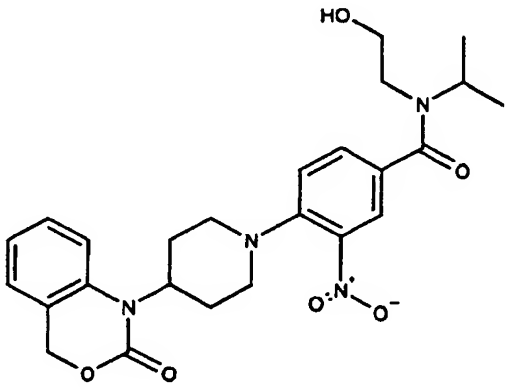


MS: APCI(+ve) 573(M+1)

Example 80

N-(2-Hydroxyethyl)-N-(1-methylethyl)-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide

[0128]

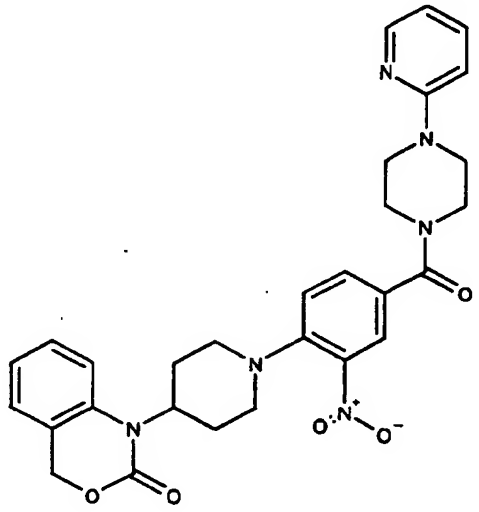


MS: APCI(+ve) 483(M+1)

Example 81

1-(1-{2-Nitro-4-[(4-pyridin-2-ylpiperazin-1-yl)carbonyl]phenyl}piperidin-4-yl)-1,4-dihydro-2H-3,1-benzoxazin-2-one

[0129]

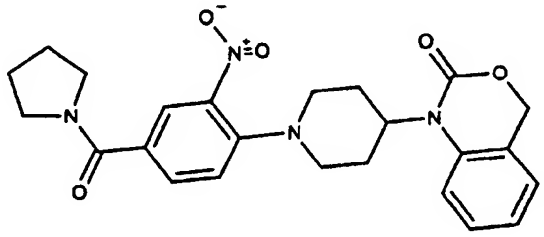


MS: APCI(+ve) 543(M+1)

Example 82

1-{1-[2-Nitro-4-(pyrrolidin-1-ylcarbonyl)phenyl]piperidin-4-yl}-1,4-dihydro-2H-3,1-benzoxazin-2-one

[0130]

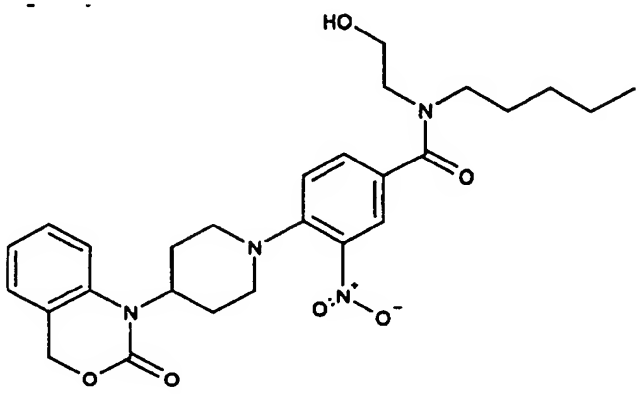


MS: APCI(+ve) 451(M+1)

Example 83

N-(2-Hydroxyethyl)-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-N-pentylbenzamide

[0131]

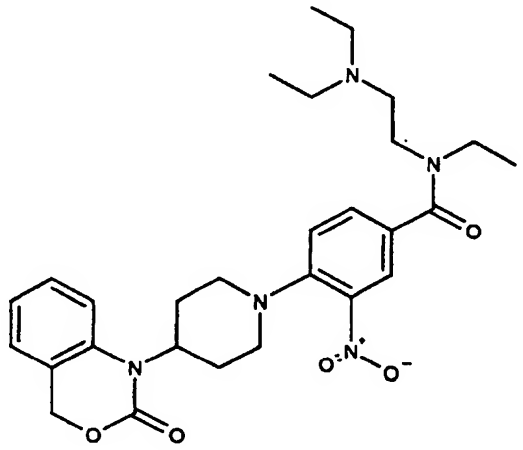


MS: APCI(+ve) 511(M+1)

Example 84

N-[2-(Diethylamino)ethyl]-N-ethyl-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide

[0132]

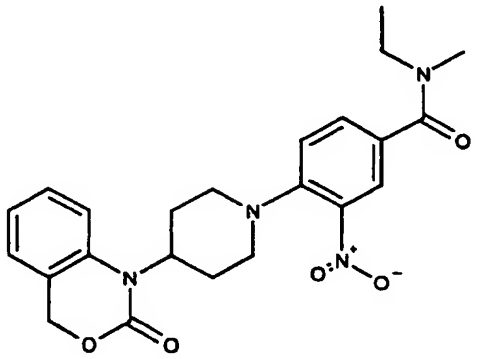


MS: APCI(+ve) 524(M+1)

Example 85

N-Ethyl-N-methyl-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide

[0133]

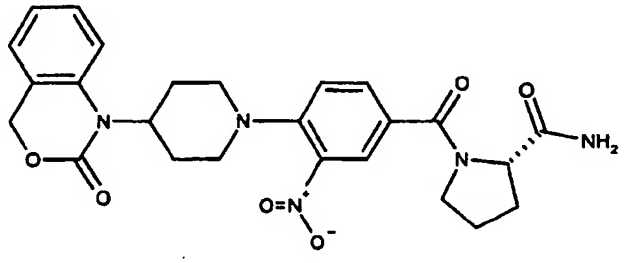


MS: APCI(+ve) 439(M+1)

Example 86

(2S)-1-({3-Nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]phenyl}carbonyl)pyrrolidine-2-carboxamide

[0134]

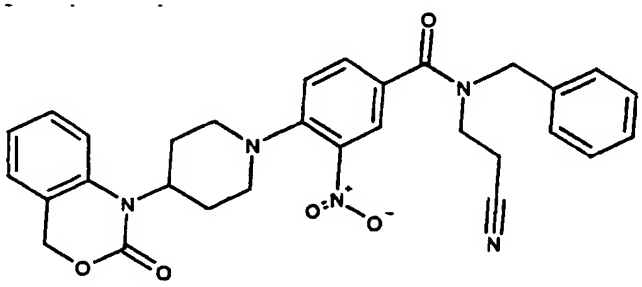


MS: APCI(+ve) 494(M+1)

Example 87

N-(2-Cyanoethyl)-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]-N-(phenylmethyl)benzamide

[0135]

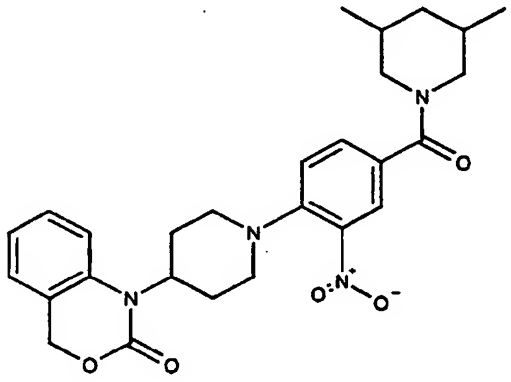


MS: APCI(+ve) 540(M+1)

Example 88

1-(1-{4-[(3,5-Dimethylpiperidin-1-yl)carbonyl]-2-nitrophenyl}piperidin-4-yl)-1,4-dihydro-2H-3,1-benzoxazin-2-one

[0136]

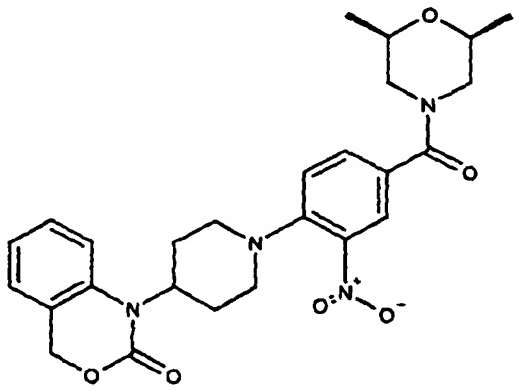


MS: APCI(+ve) 493(M+1)

Example 89

1-[1-(4-{[(2R,6S)-2,6-Dimethylmorpholin-4-yl]carbonyl}-2-nitrophenyl)piperidin-4-yl]-1,4-dihydro-2H-3,1-benzoxazin-2-one

[0137]

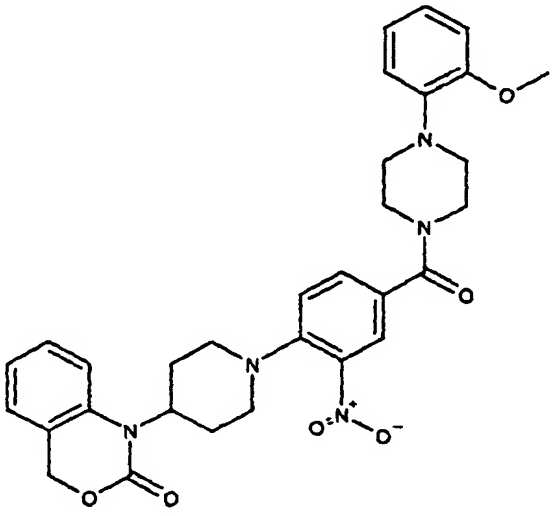


MS: APCI(+ve) 495(M+1)

Example 90

1-{1-[4-({4-[2-(Methyloxy)phenyl]piperazin-1-yl}carbonyl)-2-nitrophenyl]piperidin-4-yl}-1,4-dihydro-2H-3,1-benzoxazin-2-one

[0138]

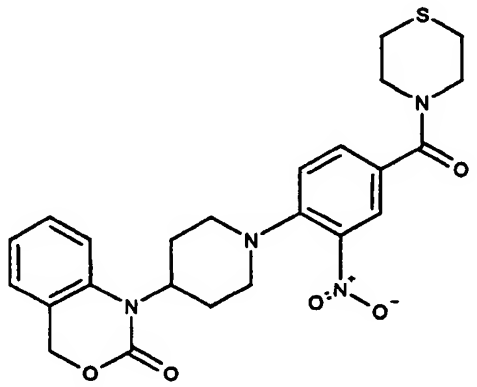


MS: APCI(+ve) 572(M+1)

Example 91

1-{1-[2-Nitro-4-(thiomorpholin-4-ylcarbonyl)phenyl]piperidin-4-yl}-1,4-dihydro-2H-3,1-benzoxazin-2-one

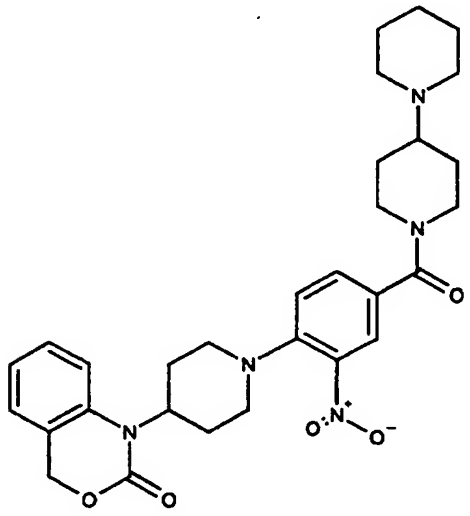
[0139]



MS: APCI(+ve) 483(M+1)

Example 92

[0140]

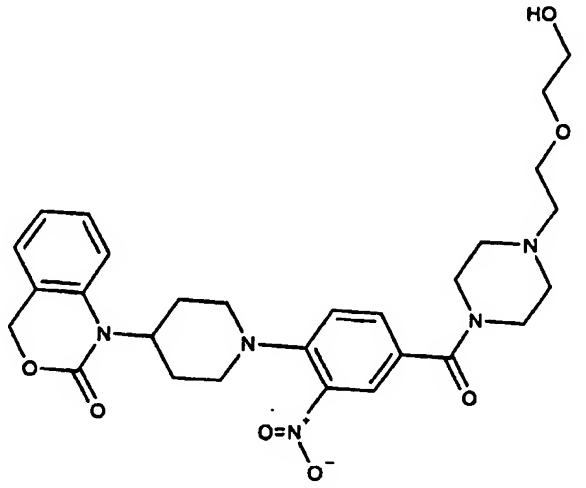


MS: APCI(+ve) 548(M+1)

Example 93

1-(1-{4-[(4-{2-[(2-Hydroxyethyl)oxy]ethyl}piperazin-1-yl)carbonyl]-2-nitrophenyl}piperidin-4-yl)-1,4-dihydro-2H-3,1-benzoxazin-2-one

[0141]

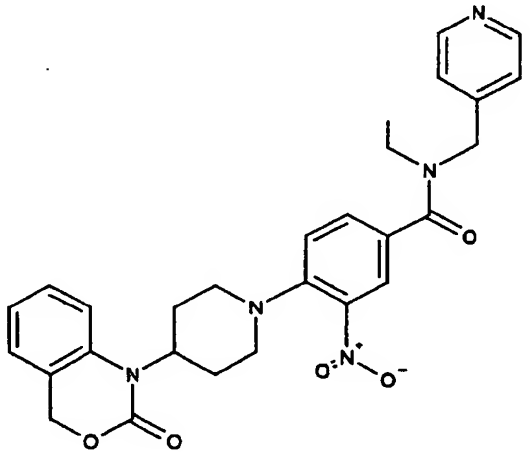


MS: APCI(+ve) 554(M+1)

Example 94

N-Ethyl-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]-N-(pyridin-4-ylmethyl)benzamide

[0142]

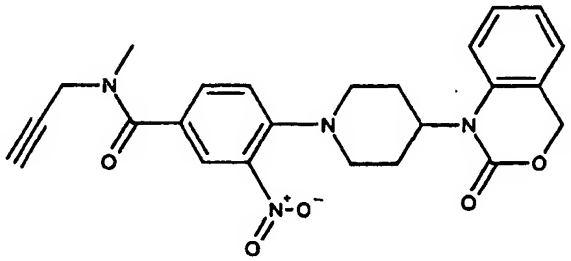


MS: APCI(+ve) 516(M+1)

Example 95

N-Methyl-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]-N-prop-2-ynylbenzamide

[0143]

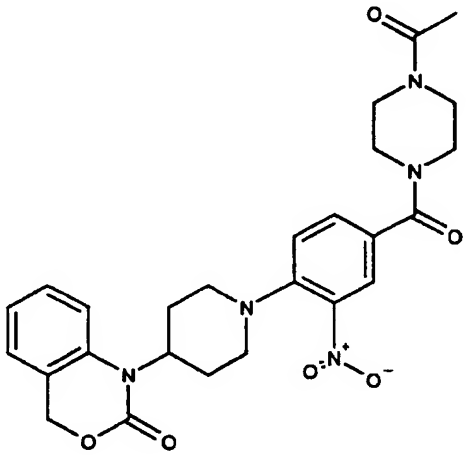


MS: APCI(+ve) 449(M+1)

Example 96

1-(1-{4-[(4-Acetylpiperazin-1-yl)carbonyl]-2-nitrophenyl}piperidin-4-yl)-1,4-dihydro-2H-3,1-benzoxazin-2-one

[0144]

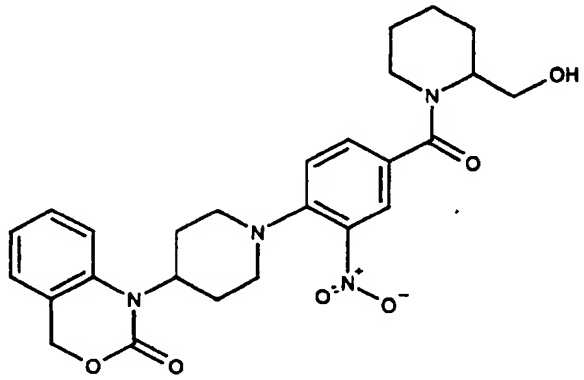


MS: APCI(+ve) 508(M+1)

Example 97

1-[1-(4-{[2-(Hydroxymethyl)piperidin-1-yl]carbonyl}-2-nitrophenyl)piperidin-4-yl]-1,4-dihydro-2H-3,1-benzoxazin-2-one

[0145]

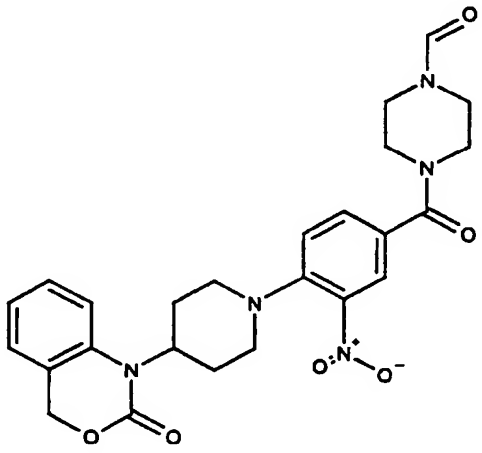


MS: APCI(+ve) 495(M+1)

Example 98

4-({3-Nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]phenyl}carbonyl)piperazine-1-carbaldehyde

[0146]

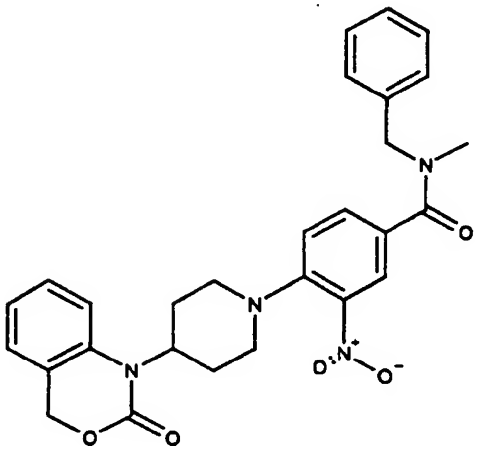


MS: APCI(+ve) 494(M+1)

Example 99

N-Methyl-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]-N-(phenylmethyl)benzamide

[0147]

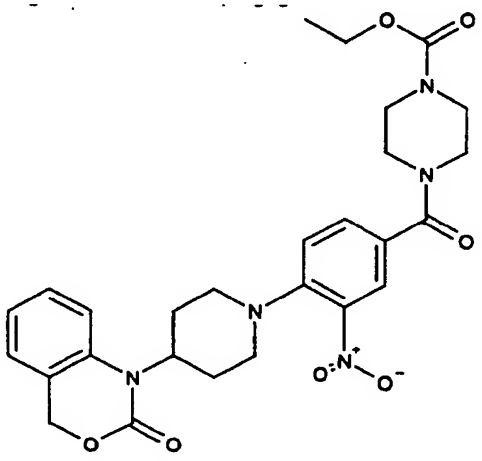


MS: APCI(+ve) 501(M+1)

Example 100

Ethyl 4-({3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]phenyl}carbonyl)piperazine-1-carboxylate

[0148]

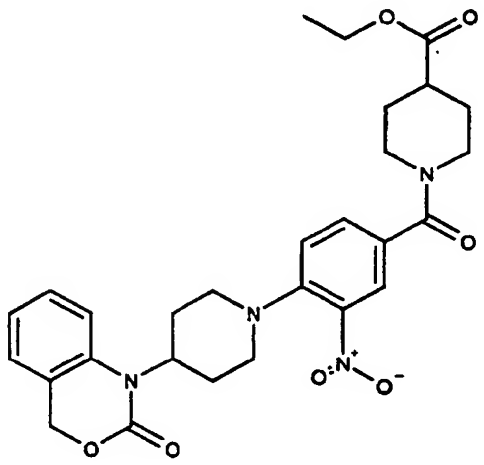


MS: APCI(+ve) 538(M+1)

Example 101

Ethyl 1-({3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]phenyl}carbonyl)piperidine-4-carboxylate

[0149]

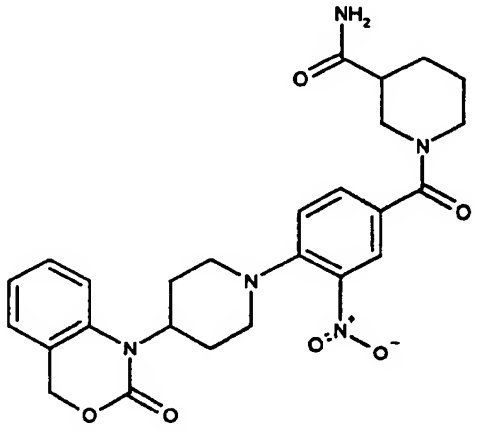


MS: APCI(+ve) 537(M+1)

Example 102

1-({3-Nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]phenyl}carbonyl)piperidine-3-carboxamide

[0150]

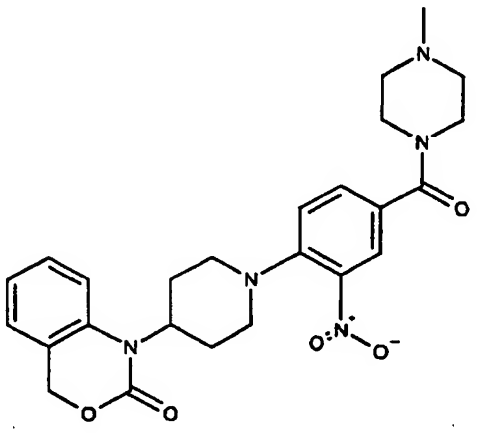


MS: APCI(+ve) 508(M+1)

Example 103

1-(1-{4-[(4-Methylpiperazin-1-yl)carbonyl]-2-nitrophenyl}piperidin-4-yl)-1,4-dihydro-2H-3,1-benzoxazin-2-one

[0151]

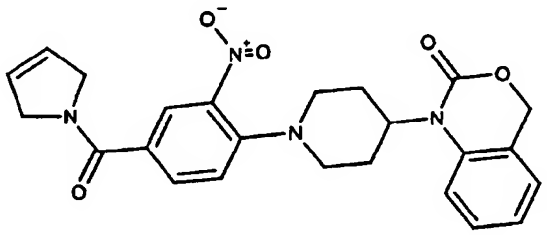


MS: APCI(+ve) 480(M+1)

Example 104

1-{1-[4-(2,5-Dihydro-1H-pyrrol-1-ylcarbonyl)-2-nitrophenyl]piperidin-4-yl}-1,4-dihydro-2H-3,1-benzoxazin-2-one

[0152]

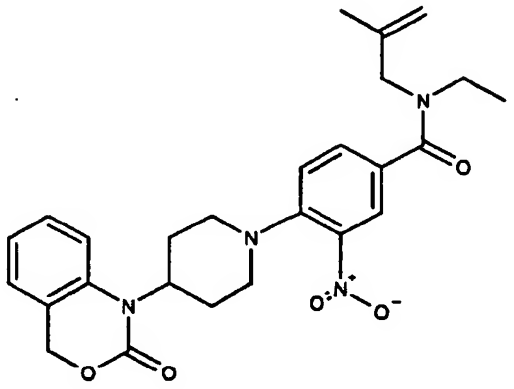


MS: APCI(+ve) 449(M+1)

Example 105

N-Ethyl-N-(2-methylprop-2-enyl)-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide

[0153]

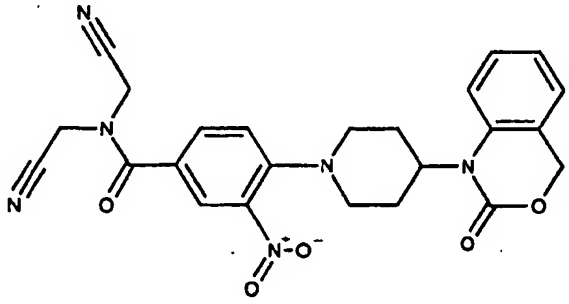


MS: APCI(+ve) 479(M+1)

Example 106

N,N-Bis(cyanomethyl)-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide

[0154]

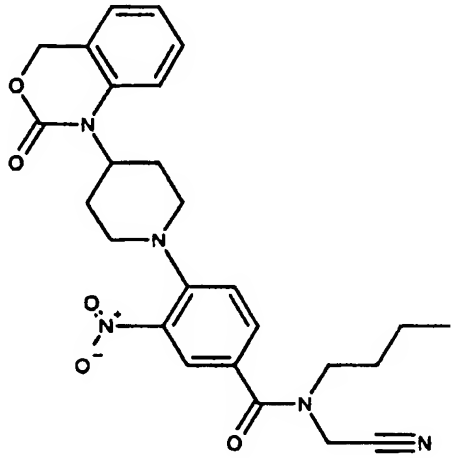


MS: APCI(+ve) 475(M+1)

Example 107

N-Butyl-N-(cyanomethyl)-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide

[0155]

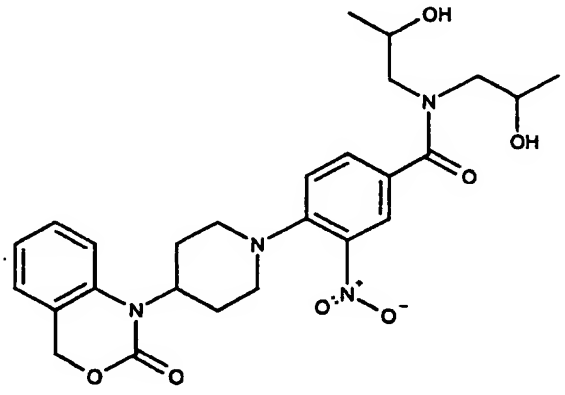


MS: APCI(+ve) 492(M+1)

Example 108

N,N-Bis(2-hydroxypropyl)-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide

[0156]

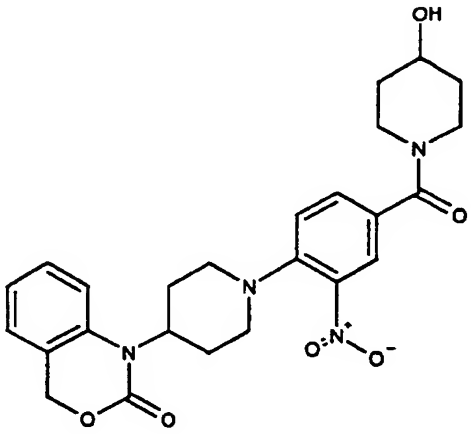


MS: APCI(+ve) 513(M+1)

Example 109

1-(1-{4-[(4-Hydroxypiperidin-1-yl)carbonyl]-2-nitrophenyl}piperidin-4-yl)-1,4-dihydro-2H-3,1-benzoxazin-2-one

[0157]

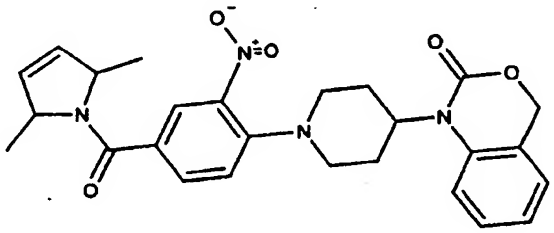


MS: APCI(+ve) 481(M+1)

Example 110

1-(1-{4-[(2,5-Dimethyl-2,5-dihydro-1H-pyrrol-1-yl)carbonyl]-2-nitrophenyl}piperidin-4-yl)-1,4-dihydro-2H-3,1-benzoxazin-2-one

[0158]

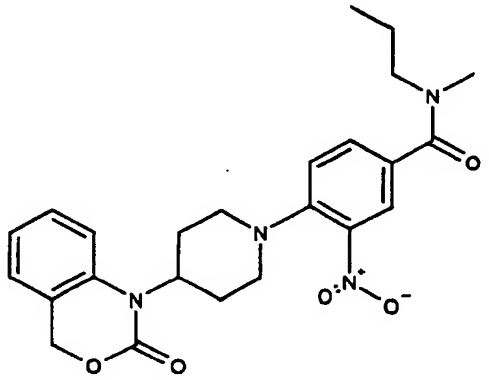


MS: APCI(+ve) 477(M+1)

Example 111

N-Methyl-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]-N-propylbenzamide

[0159]

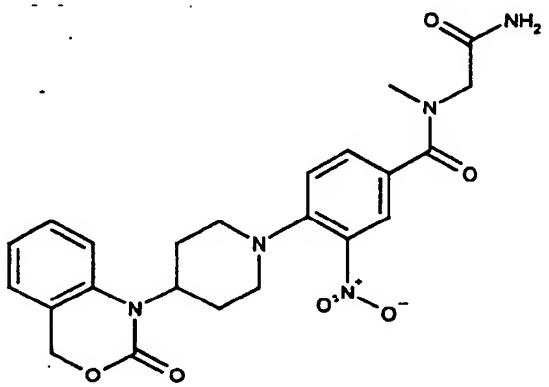


MS: APCI(+ve) 453(M+1)

Example 112

N-(2-Amino-2-oxoethyl)-N-methyl-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide

[0160]

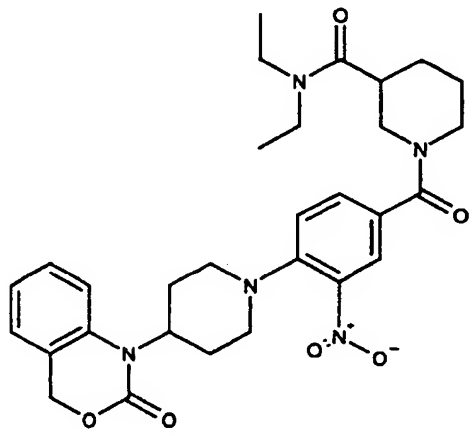


MS: APCI(+ve) 468(M+1)

Example 113

N,N-Diethyl-1-({3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]phenyl}carbonyl)piperidine-3-carboxamide

[0161]

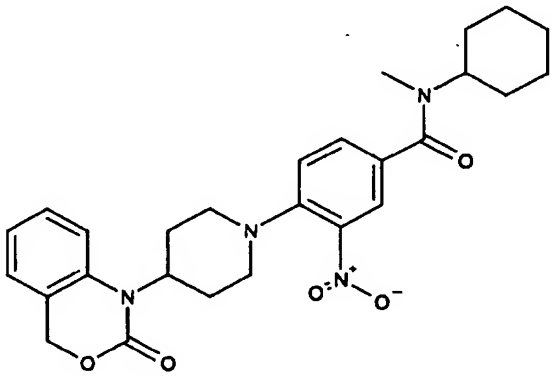


MS: APCI(+ve) 564(M+1)

Example 114

N-Cyclohexyl-N-methyl-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide

[0162]

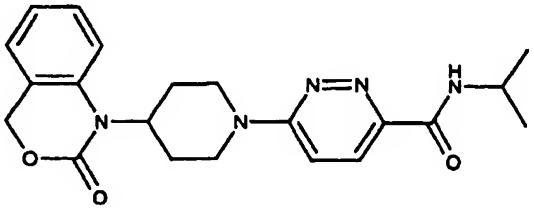


MS: APCI(+ve) 493(M+1)

Example 115

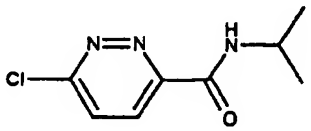
N-(1-Methylethyl)-6-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]pyridazine-3-carboxamide

[0163]



(i) 6-Chloro-N-(1-methylethyl)pyridazine-3-carboxamide

[0164]



[0165] A solution of 6-chloro-3-pyridazinecarboxylic acid (0.25g) and carbonyldiimidazole (0.282g) in N,N-dimethylformamide (10ml) was stirred at room temperature for 1h. Isopropylamine (0.162ml) was added, the mixture stirred for 3h then partitioned between ethyl acetate and water. The organic layer was washed with water, dried, and evaporated under reduced pressure. Yield 0.284g.
1H NMR: δ (DMSO-d6) 9.02(1H, d), 8.22(1H, d), 8.09(1H, d), 4.22-4.13(1H, m), 1.21(6H, d)

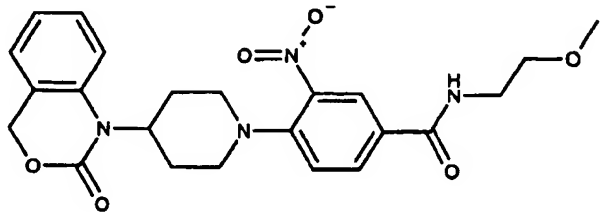
(ii) N-(1-Methylethyl)-6-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]pyridazine-3-carboxamide

[0166] 1-Piperidin-4-yl-1,4-dihydro-2H-3,1-benzoxazin-2-one hydrochloride (0.38g), the product from step (i) (0.28g) and N,N-diisopropylethylamine (0.73ml) in l-methyl-2-pyrrolidinone (6ml) was heated at 100°C for 8h. The mixture was partitioned between ethyl acetate and water, the organic layer washed with water, dried, and evaporated under reduced pressure. Purification was by chromatography eluting with 80% ethyl acetate/isohexane to yield 0.225g of a solid.
MS: APCI(+ve) 396(M+1)
1H NMR: δ (DMSO-d6) 8.51(1H, d), 7.84(1H, d), 7.45-7.35(3H, m), 7.30(1H, d), 7.13(1H, t), 5.14(2H, s), 4.64(2H, br d), 4.31-4.26(1H, m), 4.18-4.09(1H, m), 3.20(2H, t), 2.50-2.44(2H, m), 1.91(2H, br d), 1.19(6H, d)
MP:120°C

Example 116

N-[2-(Methyloxy)ethyl]-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide

[0167]

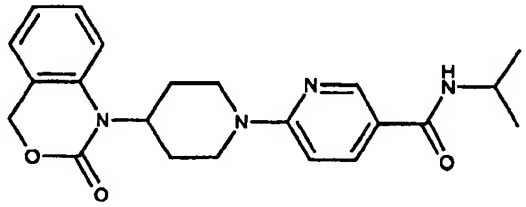


[0168] The title compound was prepared from the product of example 8 step (i) and 2-methoxyethylamine (0.5ml) using the method of example 115 step (i). Yield 0.065g.
MS: APCI(+ve) 455(M+1)
1H NMR: δ ($CDCl_3$) 8.22(1H, dd), 7.92(1H, dd), 7.37(1H, t), 7.20-7.09(4H, m), 6.46(1H,br s), 5.10(2H, s), 4.25-4.17 (1H, m), 3.68-3.47(6H, m), 3.40(3H, s), 3.15(2H, t), 2.93-2.79(2H, m), 1.95(2H, d)
MP:192-3°C

Example 117

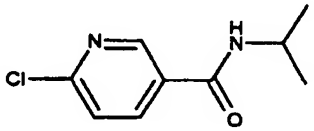
N-(1-Methylethyl)-6-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]pyridine-3-carboxamide

[0169]



(i) 6-Chloro-N-(1-methylethyl)pyridine-3-carboxamide

[0170]



[0171] The product was prepared from 6-chloro-nicotinic acid (1.0g), carbonyldiimidazole (0.8g) and isopropylamine (0.6ml) using the method of example 115 step (i). Yield 0.75g.
MS: APCI(+ve) 199(M+1)

(ii) N-(1-Methylethyl)-6-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]pyridine-3-carboxamide

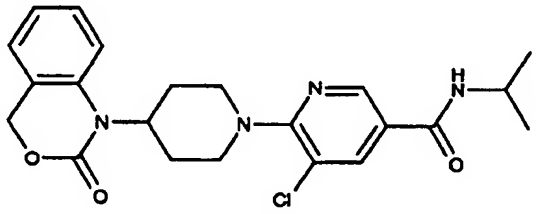
[0172] The title compound was prepared from the product of step (i) (0.4g) and 1-piperidin-4-yl-1,4-dihydro-2H-3,1-benzoxazin-2-one hydrochloride (0.5g) using the method of example 115 step (ii). Yield 0.22g.

1H NMR: δ (DMSO-d6) 8.59(1H, d), 7.97-7.94(2H, m), 7.41-7.28(3H, m), 7.12(1H, t), 6.90(1H, d), 5.13(2H, s), 4.56 (2H, br d), 4.25-4.18(1H, m), 4.12-4.00(1H, m), 3.06(2H, t), 2.50-2.38(2H, m), 1.85(2H, br d), 1.15(6H, d)
MP:>230°C

Example 118

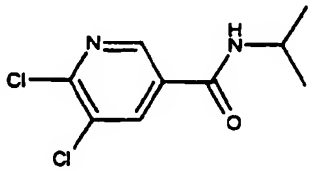
5-Chloro-N-(1-methylethyl)-6-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl] pyridine-3-carboxamide

[0173]



(i) 5,6-Dichloro-N-(1-methylethyl)pyridine-3-carboxamide

[0174]



[0175] The product was prepared from 5,6-dichloro-nicotinic acid (0.86g), carbonyldiimidazole (0.8g) and isopropylamine (0.52ml) using the method of example 115 step (i). Yield 0.69g.
MS: APCI(+ve) 199(M+1)

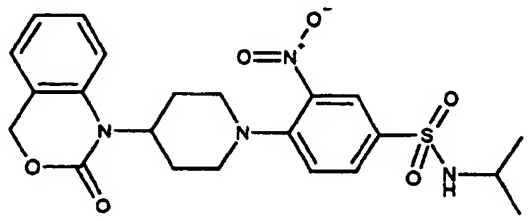
(ii) 5-Chloro-N-(1-methylethyl)-6-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]pyridine-3-carboxamide

[0176] The title compound was prepared from the product of step (i) (0.3g) and 1-piperidin-4-yl-1,4-dihydro-2H-3,1-benzoxazin-2-one hydrochloride (0.35g) using the method of example 115 step (ii). Yield 0.187g.
MS: APCI(+ve) 429(M+1)
1H NMR: δ (DMSO-d6) 8.64(1H, d), 8.25(1H, d), 8.18(1H, d), 7.40(1H, t), 7.33-7.30(2H, m), 7.12(1H, t), 5.15(2H, s), 4.18-4.02(4H, m), 3.06(2H, t), 2.71-2.60(2H, m), 1.89(2H, br d), 1.16(6H, d)
MP:216°C

Example 119

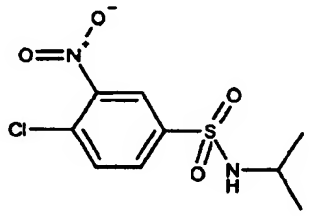
N-(1-Methylethyl)-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzenesulfonamide

[0177]



(i) 4-Chloro-N-(1-methylethyl)-3-nitrobenzenesulfonamide

[0178]



[0179] 4-Chloro-3-nitrobenzenesulfonyl chloride (2g) and isopropylamine (2.1ml) in dichloromethane (30ml) was stirred at room temperature for 2h. The mixture was washed with water, 2M hydrochloric acid, water, dried and evaporated under reduced pressure. Yield 2.2g.
1H NMR: δ (DMSO-d6) 8.45(1H, d), 8.09-7.98(3H, m), 3.39-3.31(1H, septet), 0.99(6H, d)

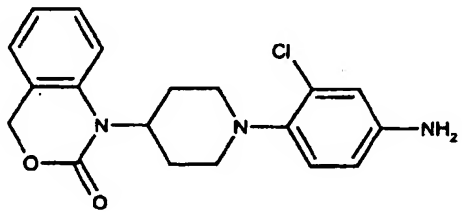
(ii) N-(1-Methylethyl)-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzenesulfonamide

[0180] The title compound was prepared from the product of step (i) (0.14g) and 1-piperidin-4-yl-1,4-dihydro-2H-3,1-benzoxazin-2-one hydrochloride (0.1g) using the method of example 115 step (ii). Yield 0.037g.
MS: APCI(+ve) 475(M+1)
1H NMR: δ (DMSO-d6) 8.17(1H, d), 7.86(1H, dd), 7.63(1H, d), 7.48(1H, d), 7.40(1H, t), 7.34-7.30(2H, m), 7.13(1H, t), 5.15(2H, s), 4.19-4.13(1H, m), 3.46(2H, d), 3.32-3.20(3H, m), 2.67-2.59(2H, m), 1.88(2H, d), 0.98(6H, d)
MP:168°C

Example120

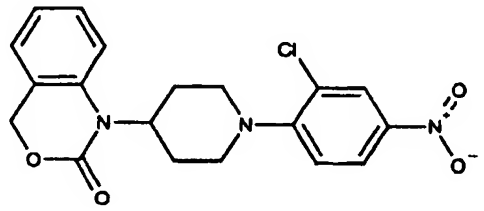
1-[1-(4-Amino-2-chlorophenyl)piperidin-4-yl]-1,4-dihydro-2H-3,1-benzoxazin-2-one

[0181]



(i) 1-[1-(2-Chloro-4-nitrophenyl)piperidin-4-yl]-1,4-dihydro-2H-3,1-benzoxazin-2-one

[0182]



[0183] The product was prepared from 1-piperidin-4-yl-1,4-dihydro-2H-3,1-benzoxazin-2-one hydrochloride (1.5g) and 3-chloro-4-fluoronitrobenzene (1.23g) using the method of example 115 step (ii). Yield 1.37g.
MS: APCI(+ve) 388(M+1)

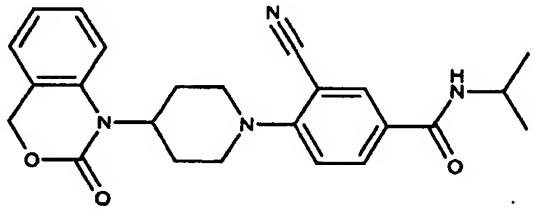
(ii) 1-[1-(4-Amino-2-chlorophenyl)piperidin-4-yl]-1,4-dihydro-2H-3,1-benzoxazin-2-one

[0184] Iron powder (1.5g) was added to a solution of the product from step (i) (1.37g) in acetic acid (50ml) and tetrahydrofuran (20ml). After stirring at room temperature for 5h, the mixture was filtered through celite, the solvent removed under reduced pressure and the residue partitioned between ethyl acetate and aqueous sodium hydrogencarbonate solution. The organic layer was washed with water, dried and evaporated under reduced pressure. Purification was by chromatography eluting with 50% ethyl acetate/isohexane. Yield 1.05g.
MS: APCI(+ve) 358(M+1)
1H NMR: δ (DMSO-d6) 7.40(1H, t), 7.29(2H, m), 7.12(1H, t), 6.92(1H, d), 6.64(1H, d), 6.49(1H, dd), 5.14(2H, s), 5.03 (2H, s), 3.98-3.92(1H, m), 3.14(2H, d), 2.77-2.62(4H, m),
1.83(2H, br d)
MP:158°C

Example 121

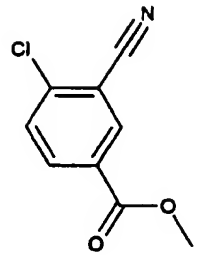
3-Cyano-N-(1-methylethyl)-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide

[0185]



(I) Methyl 4-chloro-3-cyanobenzoate

[0186]

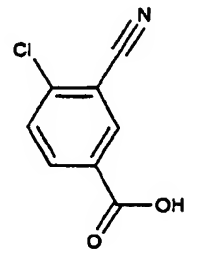


[0187] A solution of sodium nitrite (1.28g) in water (8ml) was added over 10min to a mixture of methyl 3-amino-4-chlorobenzoate (4.0g) in water (40ml) and concentrated hydrochloric acid (5ml) at 0°C. After 30min the mixture was neutralised with aqueous sodium hydroxide solution to pH~7 then added portionwise to a solution of copper cyanide (prepared from sodium cyanide (2.87g) and copper(I) chloride (2.23g) in water (40ml)) at 0°C. The mixture was stirred at room temperature for 2h then partitioned between ethyl acetate and water. The organics were washed with water, dried and evaporated under reduced pressure. The residue was triturated with 20% ethyl acetate/isohexane to yield a solid (1.55g).

1H NMR: δ ($CDCl_3$) 8.34(1H, d), 8.21-8.17(1H, m), 7.62(1H, dd), 3.96(3H, s)

(II) 4-Chloro-3-cyanobenzoic acid

[0188]

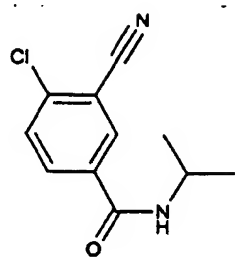


[0189] A solution of the product from step (i) (1.5g) and lithium hydroxide hydrate (0.84g) in a mixture of (1:1)water and tetrahydrofuran (40ml) was stirred at room temperature for 2h. The tetrahydrofuran was removed under reduced pressure and the residue partitioned between diethyl ether and water. The aqueous layer was acidified with 2M hydrochloric acid then extracted with ethyl acetate. The organic layer was dried and evaporated under reduced pressure. Yield 1.3g.

1H NMR: δ ($CDCl_3$) 8.42(1H, d), 8.28-8.24(1H, m), 7.67(1H, dd)

(iii) 4-Chloro-3-cyano-N-(1-methylethyl)benzamide

[0190]



[0191] The above compound was prepared from the product of step (ii) (0.6g), carbonyldiimidazole (0.59g) and isopropylamine (0.51ml) using the method of example 115 step (i). Yield 0.68g.
1H NMR: δ ($CDCl_3$) 8.06(1H, d), 7.96-7.92(1H, m), 7.59(1H, d), 5.96(1H, br s), 4.28(1H, septet), 1.29(6H, d)

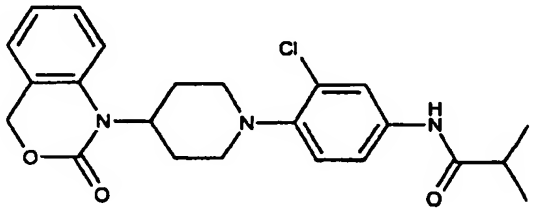
(iv) 3-Cyano-N-(1-methylethyl)-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide

[0192] The title compound was prepared from the product of step (iii) (0.29g) and 1-piperidin-4-yl-1,4-dihydro-2H-3,1-benzoxazin-2-one hydrochloride (0.3g) using the method of example 115 step (ii). Yield 0.073g.
MS: APCI(+ve) 419(M+1)
1H NMR: δ (DMSO-d6) 8.21(1H, d), 8.18(1H, d), 8.03(1H, dd), 7.40(1H, t), 7.34-7.30(2H, m), 7.22(1H, d), 7.13(1H, t), 5.16(2H, s), 4.16-4.04(2H, m), 3.81(2H, br d), 3.14(2H, t),
2.75-2.65(2H, m), 1.93(2H, br d), 1.16(6H, d)
MP:200°C

Example 122

N-{3-Chloro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]phenyl}-2-methylpropanamide

[0193]

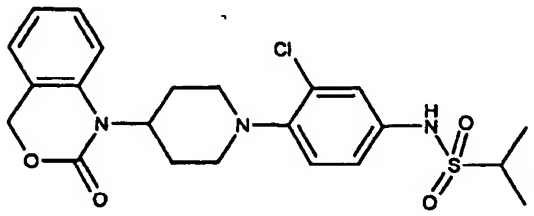


[0194] Isobutyryl chloride (0.017ml) was added to a stirred solution of the product from example 120 step (ii) (0.05g) and triethylamine (0.07ml) in dichloromethane (1ml) at room temperature. After 2h the mixture was partitioned between ethyl acetate and water, the organics separated, washed with water, dried, and evaporated under reduced pressure. Trituration with ether gave a solid, yield 0.048g.
MS: APCI(+ve) 428(M+1)
1H NMR: δ (DMSO-d6) 9.86(1H, s), 7.79(1H, d), 7.46(1H, dd), 7.42-7.38(1H, m), 7.31-7.29(2H, m), 7.14-7.10(2H, m), 5.15(2H, s), 4.04-3.98(1H, m), 3.33-2.84(2H, m), 2.82(2H, t), 2.75-2.65(2H, m), 2.59-2.50(1H, m), 1.87(2H, br d), 1.09 (6H, d)
MP:228°C

Example 123

N-{3-Chloro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]phenyl}propane-2-sulfonamide

[0195]

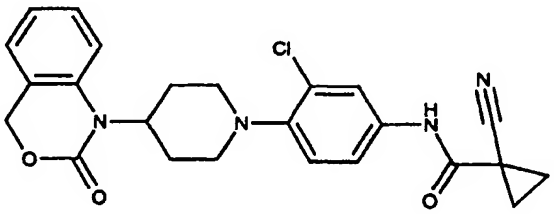


[0196] Isopropylsulphonyl chloride (0.03ml) was added to a stirred solution of the product from example 120 step (ii) (0.05g), pyridine (0.1ml) in acetonitrile (0.9ml) at room temperature. The mixture was stirred overnight, partitioned between ethyl acetate and water, the organics separated, washed with water, dried, and evaporated under reduced pressure. Purification was by chromatography eluting with 40% ethyl acetate/isohexane. Yield 0.015g.
MS: APCI(+ve) 464(M+1)
1H NMR: δ (DMSO-d6) 9.76(1H, s), 7.40(1H, t), 7.31-7.27(3H, m), 7.19-7.10(3H, m), 5.15(2H, s), 4.04-3.98(1H, m), 3.30(2H, br d), 3.25-3.18(1H, m), 2.82(2H, t), 2.74-2.65(2H, m), 1.87(2H, br d), 1.24(6H, d)
MP:175°C

Example 124

N-{3-Chloro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]phenyl}-1-cyanocyclopropanecarboxamide

[0197]

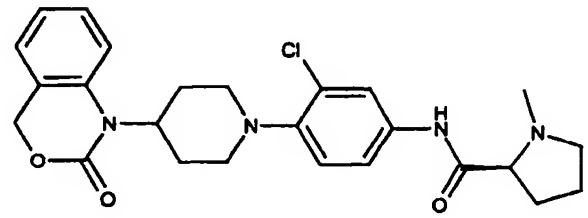


[0198] The title compound was prepared from the product of example 120 step (ii) (0.05g), carbonyldiimidazole (0.025g) and 1-cyano-1-cyclopropane carboxylic acid (0.019g) using the method of example 115 step (i). Yield 0.003g.
MS: APCI(+ve) 451(M+1)
1H NMR: δ (DMSO-d6) 10.02(1H, s), 7.70(1H, d), 7.52-7.48(1H, m), 7.40(1H, t), 7.30(2H, t), 7.17-7.10(2H, m), 5.15 (2H, s), 4.05-3.99(1H, m), 3.32(2H, d), 2.83(2H, t), 2.74-2.67(2H, m), 1.88(2H, d), 1.67(4H, s)

Example 125

(2S)-N-{3-Chloro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]phenyl}-1-methylpyrrolidine-2-carboxamide

[0199]

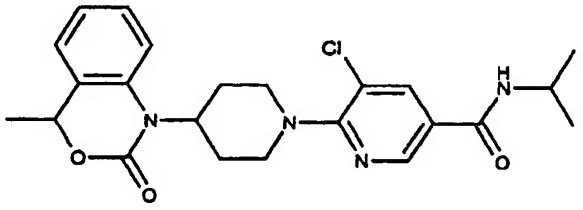


[0200] A mixture of the product from example 120 step (ii) (0.1g), N-methyl-L-proline (0.044g), N,N-diisopropylethylamine (0.17ml), 1-hydroxybenzotriazole (0.043g), 2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (0.103g) in N,N-dimethylformamide (3ml) were stirred at room temperature overnight then partitioned between ethyl acetate and water. The organic layer was washed with water, dried and evaporated under reduced pressure. Purification was by chromatography eluting with 4% methanol/dichloromethane. Yield 0.038g.
MS: APCI(+ve) 469(M+1)
1H NMR: δ (DMSO-d6) 9.73(1H, s), 7.88(1H, d), 7.59(1H, dd), 7.38(1H, t), 7.30(2H, d), 7.14-7.10(2H, m), 5.15(2H, s), 4.04-3.98(1H, m), 3.30(2H, d), 3.12-3.08(1H, m), 2.90-2.67(5H, m), 2.35-2.29(1H, m), 2.33(3H, s), 2.18-2.09(1H, m) 1.87(2H, br d), 1.82-1.75(3H, m)
MP:155°C

Example 126

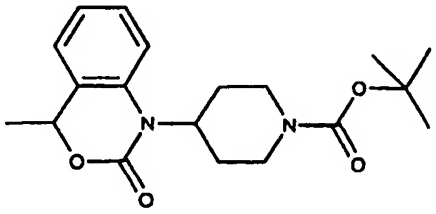
5-Chloro-N-(1-methylethyl)-6-[4-(4-methyl-2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]pyridine-3-carboxamide

[0201]



(i) 1,1-Dimethylethyl 4-(4-methyl-2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidine-1-carboxylate

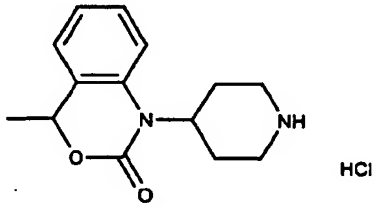
[0202]



[0203] Acetic acid (1ml) was added dropwise to a solution of N-tert-butoxycarbonyl-4-piperidone (9.4g), 1-(2-aminophenyl)-ethanol (4.3g) and sodium cyanoborohydride (10g) in dichloromethane and the mixture stirred at room temperature overnight. The mixture was partitioned between ethyl acetate and water, the organics separated and washed with aqueous sodium hydrogencarbonate solution, water, dried, and evaporated under reduced pressure. The crude product was dissolved in tetrahydrofuran (100ml) and N,N-diisopropylethylamine (23ml), cooled to 0°C, then triphosgene (4.3g) added. The mixture was warmed to room temperature and stirred overnight. The mixture was partitioned between ethyl acetate and water, the organics washed with water, dried and evaporated under reduced pressure. Purification was by chromatography eluting with 20% ethyl acetate/isohexane. Yield 1.4g.
MS: APCI(+ve) 247(M+1-Boc)

(ii) 4-Methyl-1-piperidin-4-yl-1,4-dihydro-2H-3,1-benzoxazin-2-one hydrochloride

[0204]



[0205] 4M Hydrogen chloride in 1,4-dioxane (20ml) was added to a solution of the product from step (i) (1.4g) in 1,4-dioxane (20ml) and the mixture stirred at room temperature overnight. The solvent was removed under reduced pressure and the residue triturated with ether. Yield 1.0g.
MS: APCI(+ve) 247(M+1)

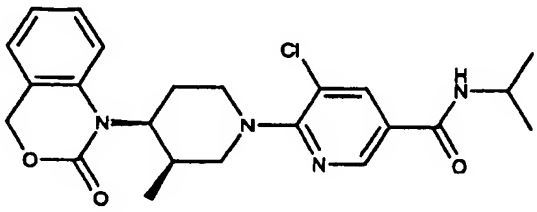
(iii) 5-Chloro-N-(1-methylethyl)-6-[4-(4-methyl-2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]pyridine-3-carboxamide

[0206] The title compound was prepared from the product of step (ii) (0.36g) and the product from example 117 step (i) (0.466g) using the method of example 115 step (ii). Yield 0.112g
MS: APCI(+ve) 443(M+1)
1H NMR: δ (DMSO-d6) 8.64(1H, d), 8.25(1H, d), 8.18(1H, d), 7.42-7.38(1H, m), 7.34-7.27(2H, m), 7.16-7.12(1H, m), 5.36(1H, q), 4.18-4.05(4H, m), 3.09-3.02(2H, m), 2.72-2.61(2H, m), 1.89(2H, br d), 1.57(3H,d), 1.16(6H, d)

Examples 127

±-5-Chloro-N-(1-methylethyl)-6-[(cis)-3-methyl-4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]pyridine-3-carboxamide hydrochloride

[0207]

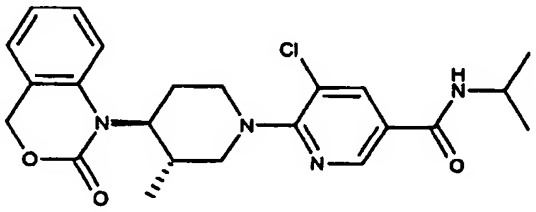


HCl

Example 128

±-5-Chloro-N-(1-methylethyl)-6-[(trans)-3-methyl-4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]pyridine-3-carboxamide hydrochloride

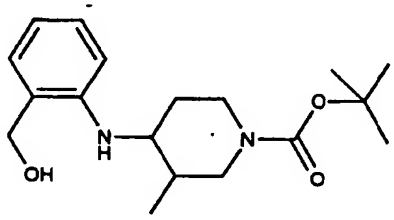
[0208]



HCl

(I) 1,1-Dimethylethyl 4-{[2-(hydroxymethyl)phenyl]amino}-3-methylpiperidine-1-carboxylate

[0209]

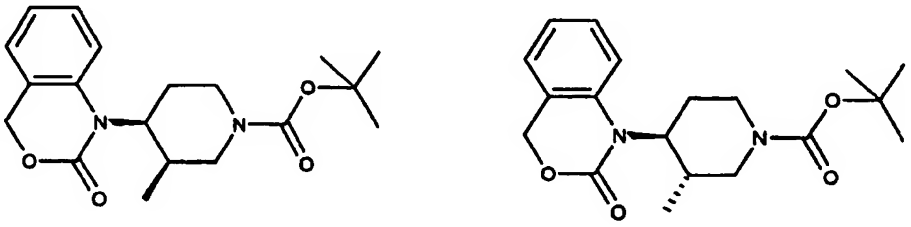


[0210] The product was prepared from N-tert-butoxycarbonyl-3-methyl-4-piperidone (4.3g) and 2-amino-benzyl alcohol (2.59g) using the method of example 7 step (i). Yield 6.3g as a mixture of diastereoisomers.
MS: APCI(+ve) 320(M+1)

(ii) ±-1,1-Dimethylethyl (cis)-3-methyl-4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidine-1-carboxylate

±-1,1-Dimethylethyl (trans)-3-methyl-4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidine-1-carboxylate

[0211]



[0212] The above compounds were prepared from the product of step (i) (6.3g) using the method of example 7 step (ii). Cis and trans diastereoisomers were separated (relative stereochemistry).

[0213] ±-1,1-Dimethylethyl (cis)-3-methyl-4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidine-1-carboxylate, yield 0.24g MS: APCI(+ve) 247(M+1)

[0214] ±-1,1-Dimethylethyl (trans)-3-methyl-4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidine-1-carboxylate, yield 0.68g MS: APCI(+ve) 247(M+1)

(iii) ±-5-Chloro-N-(1-methylethyl)-6-[(cis)-3-methyl-4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl] pyridine-3-carboxamide hydrochloride

[0215] ±-1,1-Dimethylethyl (cis)-3-methyl-4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidine-1-carboxylate (0.24g) was dissolved in 4M hydrogen chloride in 1,4-dioxane (5ml) stirred at room temperature for 4h, then evaporated under reduced pressure. The product was dissolved in 1-methyl 2-pyrrolidinone (10ml), N,N-diisopropylethylamine (0.5ml) and the product from example 117 step (i) (0.23g) added. The mixture was heated at 100°C for 12h, partitioned between ethyl acetate and water, the organics separated, dried and evaporated under reduced pressure. Purification was by chromatography eluting with 30-40% ethyl acetate/isohexane. The hydrochloride salt was made from ethereal hydrogen chloride. Yield 0.07g.
MS: APCI(+ve) 443(M+1)
1H NMR: δ (DMSO-d6) 8.64(1H, d), 8.27(1H, d), 8.19(1H, d), 7.41-7.30(3H, m), 7.12(1H, t), 6.12(2H, br s), 5.22-5.14 (2H, m), 4.12-3.99(3H, m), 3.77(1H, br s), 3.13(1H, br t), 2.86(1H, br s), 2.75-2.50(2H, m), 1.94(1H, br d), 1.16(6H, d), 0.87(3H, d)
MP:215°C

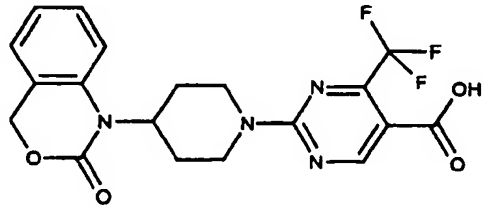
±-5-chloro-N-(1-methylethyl)-6-[(trans)-3-methyl-4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]pyridine-3-carboxamide hydrochloride

[0216] The titled compound was prepared from ±-1,1-dimethylethyl (trans)-3-methyl-4-(2-oxo-2H-3,1-benzoxazin-1 (4H)-yl)piperidine-1-carboxylate (0.68g) using the same method as step (iii). Yield 0.219g.
MS: APCI(+ve) 443(M+1)
1H NMR: δ (DMSO-d6) 8.63(1H, s), 8.25(1H, d), 8.17(1H, s), 7.40-7.29(2H, m), 7.28(1H, d), 7.12(1H, t), 6.04(2H, br s), 5.21-5.13(2H, m), 4.29-4.24(1H, m), 4.12-3.91(3H, m), 3.30(1H, dd), 3.18-3.02(2H, m), 2.56-2.54(1H, m), 1.87(1H, br d), 1.16(6H, d), 1.09(3H, d)
MP:195°C

Examples 129-144

(I) 2-[4-(2-Oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]-4-(trifluoromethyl)pyrimidine-5-carboxylic acid

[0217]



[0218] The title compound was prepared from 1-piperidin-4-yl-1,4-dihydro-2H-3,1-benzoxazin-2-one hydrochloride (0.70g) and 2-chloro-4-(trifluoromethyl)pyrimidine-5-carboxylic acid (1.8g) using the method of example 115 step (ii). Yield 1.1g.
MS: APCI(+ve) 423(M+1)

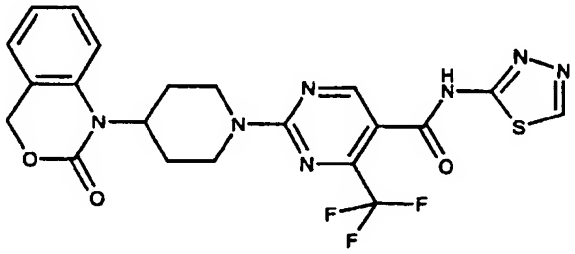
(II) Examples 129-144

[0219] Oxalyl chloride (0. 1ul) was added to a solution of the product from step (i) (0.27g) in dichloromethane (10ml) and stirred at room temperature for 3h. The solvent was removed under reduced pressure and the residue dissolved in 1-methyl-2-pyrrolidinone. An aliquot of the solution of the acid chloride (0.1ml), the appropriate amine (2 equivalents) and triethylamine (5 equivalents) in 1-methyl-2-pyrrolidinone (0.03ml) were left at room temperature for 24h. The reaction mixture was evaporated to dryness and the residue dissolved in dimethylsulphoxide (0.4ml).

Example 129

2-[4-(2-Oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]-N-(1,3,4-thiadiazol-2-yl)-4-(trifluoromethyl)pyrimidine-5-carboxamide

[0220]

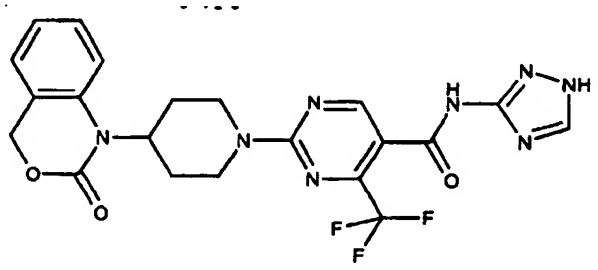


MS: APCI(+ve) 505(M+1)

Example 130

2-[4-(2-Oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]-N-(1H-1,2,4-triazol-3-yl)-4-(trifluoromethyl)pyrimidine-5-carboxamide

[0221]

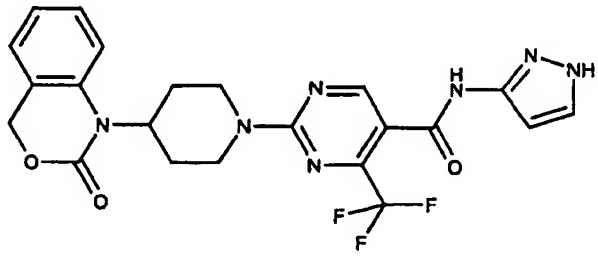


MS: APCI(+ve) 488(M+1)

Example 131

2-[4-(2-Oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]-N-(1H-pyrazol-3-yl)-4-(trifluoromethyl)pyrimidine-5-carboxamide

[0222]

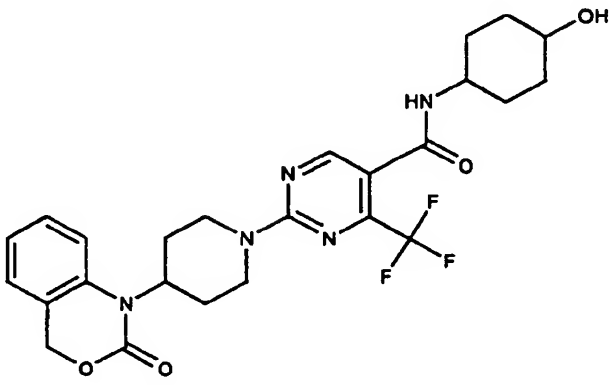


MS: APCI(+ve) 487(M+1)

Example 132

N-(4-Hydroxycyclohexyl)-2-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]-4-(trifluoromethyl)pyrimidine-5-carboxamide

[0223]

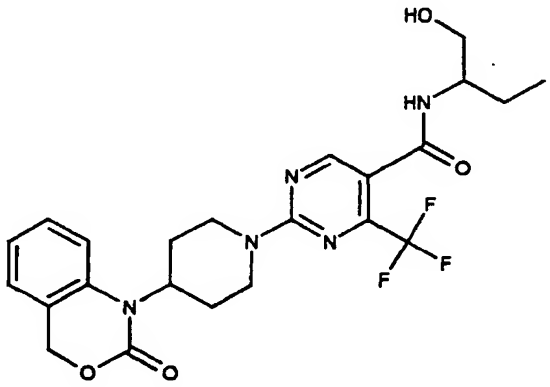


MS: APCI(+ve) 519(M+1)

Example 133

N-[1-(Hydroxymethyl)propyl]-2-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]-4-(trifluoromethyl) pyrimidine-5-carboxamide

[0224]

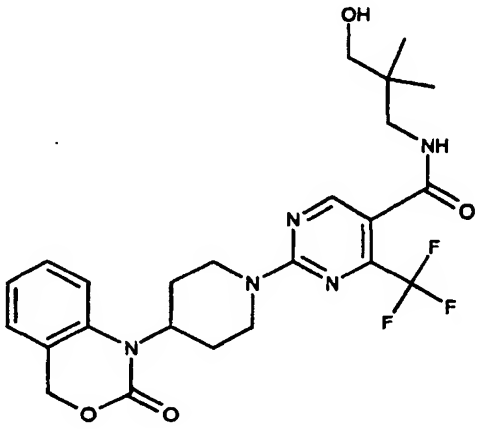


MS: APCI(+ve) 493(M+1)

Example 134

N-(3-Hydroxy-2,2-dimethylpropyl)-2-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]-4-(trifluoromethyl) pyrimidine-5-carboxamide

[0225]

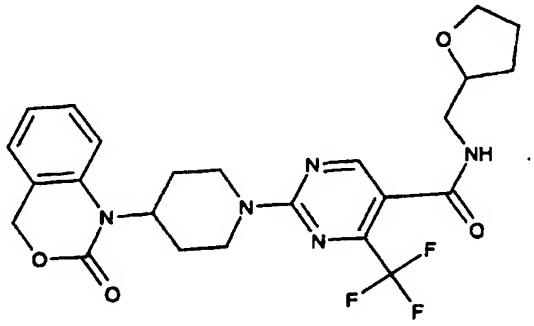


MS: APCI(+ve) 507 (M+1)

Example 135

2-[4-(2-Oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]-N-(tetrahydrofuran-2-ylmethyl)-4-(trifluoromethyl) pyrimidine-5-carboxamide

[0226]

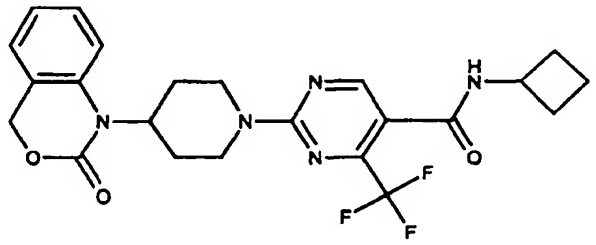


MS: APCI(+ve) 505(M+1)

Example 136

N-Cyclobutyl-2-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]-4-(trifluoromethyl)pyrimidine-5-carboxamide

[0227]

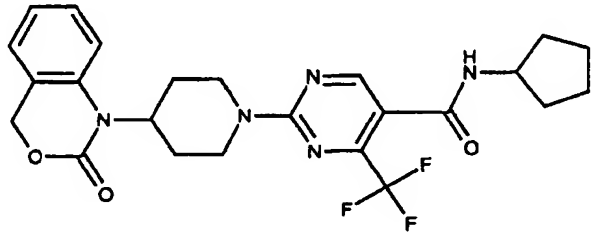


MS: APCI(+ve) 475(M+1)

Example 137

N-Cyclopentyl-2-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]-4-(trifluoromethyl)pyrimidine-5-carboxamide

[0228]

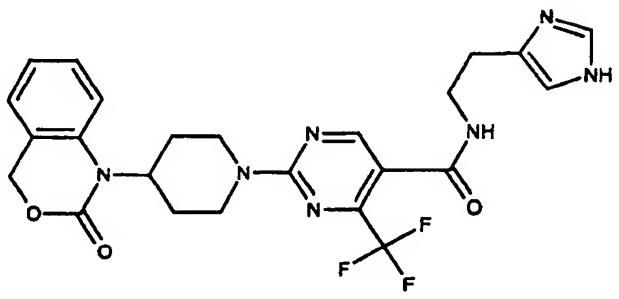


MS: APCI(+ve) 489(M+1)

Example 138

N-[2-(1H-Imidazol-4-yl)ethyl]-2-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]-4-(trifluoromethyl) pyrimidine-5-carboxamide

[0229]

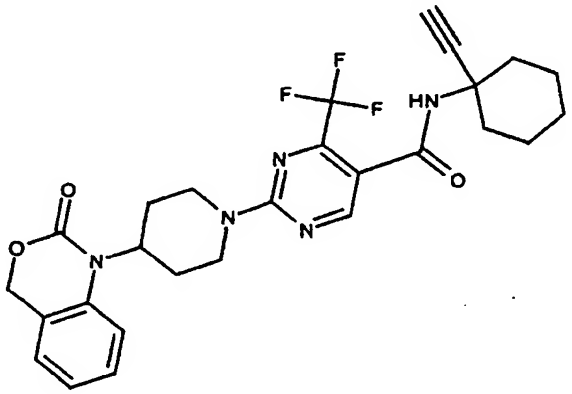


MS: APCI(+ve) 515(M+1)

Example 139

N-(1-Ethynylcyclohexyl)-2-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]-4-(trifluoromethyl)pyrimidine-5-carboxamide

[0230]

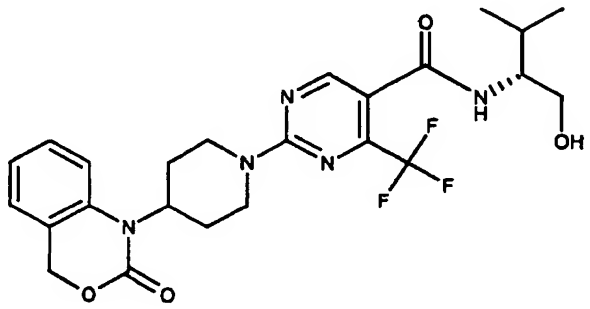


MS: APCI(+ve) 527(M+1)

Example 140

N-[(1R)-1-(Hydroxymethyl)-2-methylpropyl]-2-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]-4-(trifluoromethyl)pyrimidine-5-carboxamide

[0231]

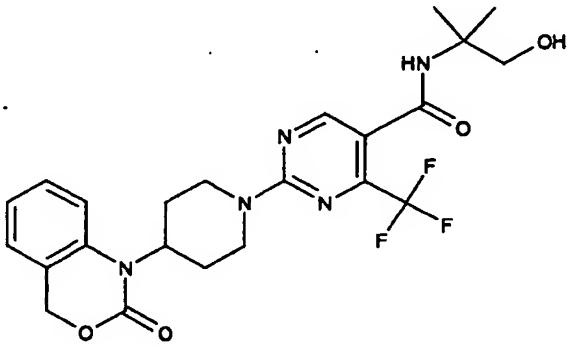


MS: APCI(+ve) 507(M+1)

Example 141

N-(2-Hydroxy-1,1-dimethylethyl)-2-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]-4-(trifluoromethyl) pyrimidine-5-carboxamide

[0232]

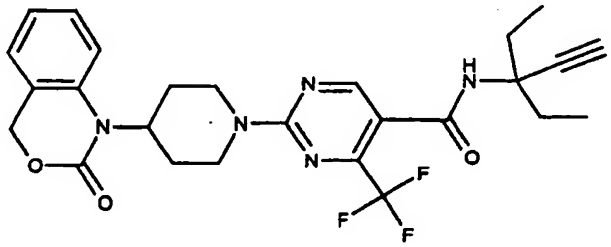


MS: APCI(+ve) 493(M+1)

Example 142

N-(1,1-Diethylprop-2-ynyl)-2-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]-4-(trifluoromethyl) pyrimidine-5-carboxamide

[0233]

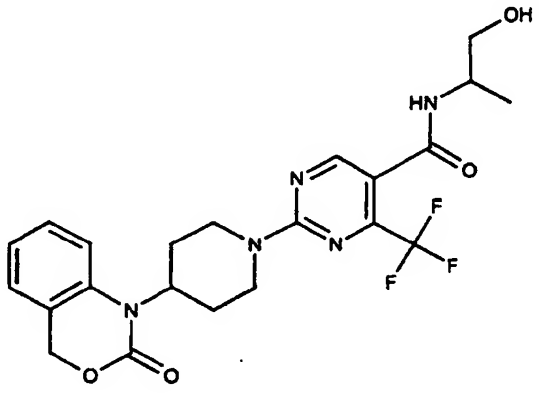


MS: APCI(+ve) 515(M+1)

Example 143

N-(2-Hydroxy-1-methylethyl)-2-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]-4-(trifluoromethyl) pyrimidine-5-carboxamide

[0234]

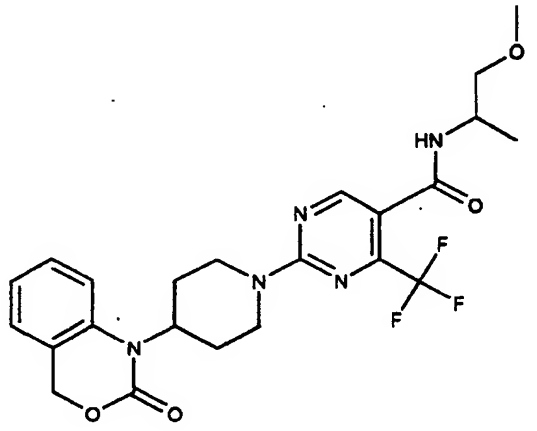


MS: APCI(+ve) 479(M+1)

Example 144

N-[1-Methyl-2-(methyloxy)ethyl]-2-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]-4-(trifluoromethyl) pyrimidine-5-carboxamide

[0235]

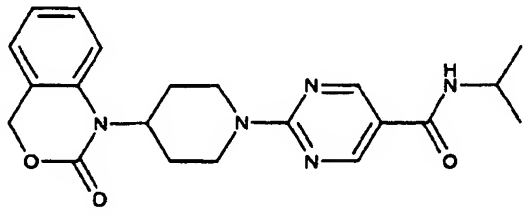


MS: APCI(+ve) 493(M+1)

Example 145

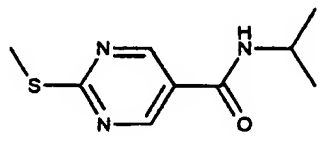
N-(1-Methylethyl)-2-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]pyrimidine-5-carboxamide

[0236]



(i) N-(1-Methylethyl)-2-(methylthio)pyrimidine-5-carboxamide

[0237]



[0238] The product was prepared from N-(1-methylethyl)-2-(methylthio)pyrimidine-5-carboxylic acid (Acta Chem Scand., Ser.B (1986), B40(9), 764-767.) (0.78g), carbonyldiimidazole (0.82g) and isopropylamine (0.3g) using the method of example 115 step (i). Yield 0.66g.

MS: APCI(+ve) 212 (M+1)

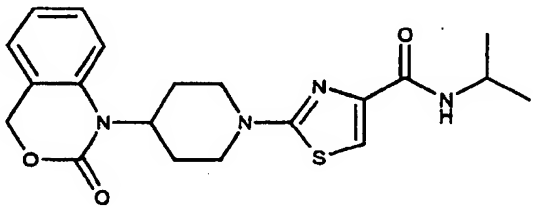
(II) N-(1-Methylethyl)-2-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl] pyrimidine-5-carboxamide

[0239] The product from step (i) (0.66g) was dissolved in chloroform (50ml) and to this solution was added 3-chloroperoxybenzoic acid (2.02g). The mixture was stirred for 1h at room temperature before being washed with an aqueous solution of sodium metabisulphite followed by aqueous sodium bicarbonate. The organic layer was dried and evaporated under reduced pressure. The residue was dissolved in 1-methyl-2-pyrrolidinone (4ml) and this solution treated with *N,N*-diisopropylethylamine (0.5ml) followed by 1-piperidin-4-yl-1,4-dihydro-2H-3,1-benzoxazin-2-one hydrochloride (0.2g) before being heated at 60°C for 2h. The mixture was partitioned between water and ethyl acetate, the organic layer washed with water, dried and evaporated under reduced pressure. Purification was by chromatography eluting with ethyl acetate/isohexane (2/1). Yield 0.03g as a solid.
MS: APCI(+ve) 396 (M+1)
1H NMR: δ (DMSO-d6) 8.77(2H, s), 8.07(1H, d), 7.41-7.29(3H, m), 7.12(1H, t), 5.14(2H, s), 4.88(2H, d), 4.28-4.22(1H, m), 4.11-4.02(1H, m), 3.12(2H, t), 2.45-2.33(2H, m), 1.89(2H, d), 1.16(6H, d)
MP:236-239°C

Example 146

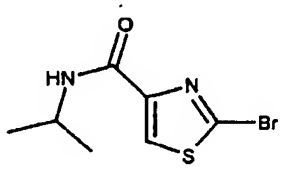
N-(1-Methylethyl)-2-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]-1,3-thiazole-4-carboxamide

[0240]



(i) 2-Bromo-N-(1-methylethyl)-1,3-thiazole-4-carboxamide

[0241]



[0242] The product was prepared from 2-bromo-N-(1-methylethyl)-1,3-thiazole-4-carboxylic acid (WO 9848799) (0.77g), carbonyldiimidazole (0.66g) and isopropylamine (0.24g) using the method of example 115 step (i). Yield 0.82g.
1H NMR: δ (DMSO-d6) 8.25(1H, s), 8.24-8.18(1H, m), 4.14-4.02(1H, m), 1.16(6H, d)

(ii) N-(1-Methylethyl)-2-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]-1,3-thiazole-4-carboxamide

[0243] The title compound was prepared from the product of step (i) (0.16g) and 1-piperidin-4-yl-1,4-dihydro-2H-3,1-benzoxazin-2-one hydrochloride (0.15g) using the method of example 115 step (ii). Yield 0.04g.
MS: APCI(+ve) 401 (M+1)
1H NMR: δ (DMSO-d6) 7.68(1H, d), 7.43-7.29(4H, m), 7.13(1H, t), 5.16(2H, s), 4.22-3.99(4H, m), 3.29-3.18(2H, m), 2.64-2.49(2H, m), 1.91(2H, d), 1.16(6H, d)
MP:214-215°C

Example 147

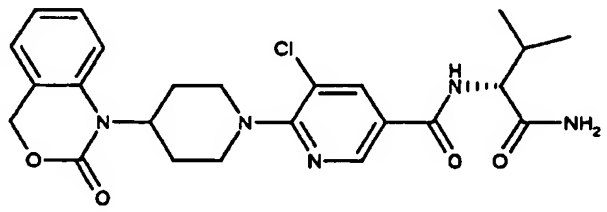
N-(1-Methylethyl)-3-(methylsulfonyl)-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide

[0244] 4-Fluoro-N-(1-methylethyl)-3-(methylsulfonyl)benzoic acid (J.Med.Chem (1997), 40(13), 2017-2034) (0.45g) was reacted with carbonyldiimidazole (0.37g) and isopropylamine (0.25g) using the method of example 115 step (i) to yield the corresponding amide. Yield 0.50g.
A solution of this amide (0.50g) in 1-methyl-2-pyrrolidinone (10ml) was treated with 1-piperidin-4-yl-1,4-dihydro-2H-3,1-benzoxazin-2-one hydrochloride (0.40g) followed by *N,N*-diisopropylethylamine (0.73g) and the resultant mixture heated at 100°C for 14h. The mixture was then partitioned between water and ethyl acetate, the organic layer washed with water, dried and evaporated under reduced pressure. The resultant solid was washed with ethyl acetate (10ml) followed by ethanol (1ml) to yield the desired product as a solid (0.13g).
MS: APCI(+ve) 472 (M+1)
1H NMR: δ (DMSO-d6) 8.47(1H, d), 8.38(1H, d), 8.16(1H, d), 7.63(1H, d), 7.42(1H, t), 7.32-7.29(2H, m), 7.13(1H, t), 5.16(2H, s), 4.14-4.05(2H, m), 3.49(3H, s), 3.32-3.29(2H, m), 3.03(2H, t), 2.83-2.76(2H, m), 1.91-1.88(2H, m), 1.17 (6H, d)
MP:240-242°C

Example 148

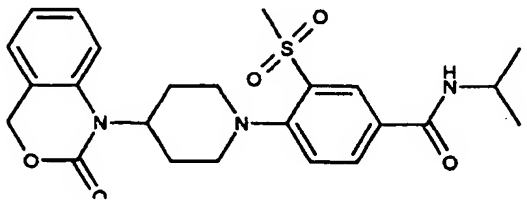
N-[(1R)-1-(Aminocarbonyl)-2-methylpropyl]-5-chloro-6-[4-(2-oxo-2H-3,1-benzoxazin-1 (4H)-yl)piperidin-1-yl] pyridine-3-carboxamide

[0245]



(i) 5-Chloro-6-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]pyridine-3-carboxylic acid

[0246] The title compound was prepared from 5,6-dichloronicotinic acid (2.2g) and 1-piperidin-4-yl-1,4-dihydro-2H-3,1-benzoxazin-2-one hydrochloride (3.0g) using the method of example 115 step (ii). Yield 0.037g
MS: APCI(+ve) 388 (M+1)



(ii) N-[(1R)-1-(Aminocarbonyl)-2-methylpropyl]-5-chloro-6-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl] pyridine-3-carboxamide

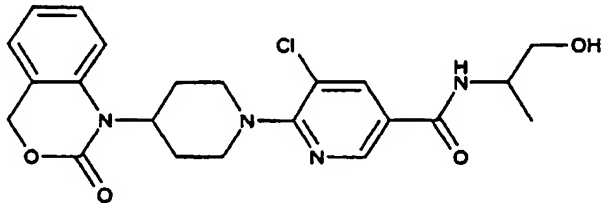
[0247] The product of step (i) (0.14g) was dissolved in 1-methyl-2-pyrrolidinone (4ml) and to this solution was added carbonyldiimidazole (0.064g) the mixture was stirred at room temperature for 1h and then treated with D-valinamide hydrochloride (0.1 1g) and *N,N*-diisopropylethylamine (0.10g). After stirring for 18h at room temperature the mixture was partitioned between aqueous sodium bicarbonate and ethyl acetate, the organic layer was washed with water,

dried and evaporated under reduced pressure. The resultant solid was washed with ethyl acetate to yield 0.06g of product.
MS: APCI(+ve) 486 (M+1)
1H NMR: δ (DMSO-d6) 8.68(1H, d), 8.31-8.27(2H, m), 7.46(1H, s), 7.42-7.29(3H, m), 7.13(1H, t), 7.06(1H, s), 5.15 (2H, s), 4.26(1H, t), 4.19-4.04(3H, m), 3.07(2H, t), 2.72-2.60(2H, m), 2.14-2.07(1H, m), 1.90(2H, d), 0.94-0.91(6H, m)
MP:140-143°C

Example 149

5-Chloro-N-(2-hydroxy-1-methylethyl)-6-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]pyridine-3-carboxamide

[0248]

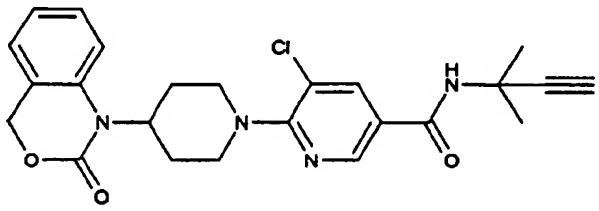


[0249] The title compound was prepared from the product of example 148 step (i) (0.14g), carbonyldiimidazole (0.064g) and DL-2-amino-1-propanol (0.05g) using the method of example 115 step (i). Purification was by chromatography eluting with 20% ethyl acetate/isohexane. Yield 0.04g as a solid.
MS: APCI(+ve) 445 (M+1)
1H NMR: δ (DMSO-d6) 8.64(1H, d), 8.20(1H, d), 8.15(1H, d), 7.42-7.29(3H, m), 7.12(1H, t), 5.15(2H, s), 4.72(1H, t), 4.15-3.98(4H, m), 3.48-3.37(2H, m), 3.06(2H, t), 2.73-2.63(2H, m), 1.89(2H, d), 1.13-1.09(3H, m)
MP:125-128°C

Example 150

5-Chloro-N-(1,1-dimethylprop-2-ynyl)-6-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]pyridine-3-carboxamide

[0250]

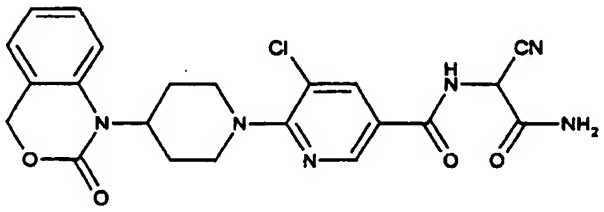


[0251] The title compound was prepared from the product of example 148 step (i) (0.14g), carbonyldiimidazole (0.064g) and 1,1-dimethylpropargylamine (0.06g) using the method of example 115 step (i). Purification was by chromatography eluting with ethyl acetate/isohexane (2/3). Yield 0.03g as a solid.
MS: APCI(+ve) 453 (M+1)
1H NMR: δ (DMSO-d6) 8.62(1H, d), 8.29(1H, s), 8.18(1H, d), 7.42-7.29(3H, m), 7.12(1H, t), 5.15(2H, s), 4.19-4.07(3H, m), 3.12(1H, s), 3.07(2H, t), 2.72-2.60(2H, m), 1.90(2H, d),
1.60(6H, s)
MP:135-138°C

Example 151

N-(2-Amino-1-cyano-2-oxoethyl)-5-chloro-6-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]pyridine-3-carboxamide

[0252]

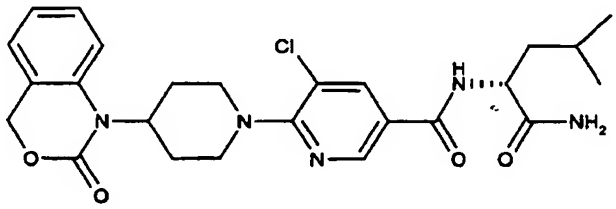


[0253] The product of example 148 step (i) (0.14g) was stirred as a suspension in dichloromethane (4ml) and to this mixture was added oxalyl chloride (0.05g) followed by *N,N*-dimethylformamide (0.01g). After stirring for 1h at room temperature the mixture was treated with 2-aminocyanoacetamide (0.14g) 1-methyl-2-pyrrolidinone (3ml) and then *N, N*-diisopropylethylamine (1ml), stirring was then continued for a further 18h at room temperature. The reaction mixture was partitioned between aqueous sodium bicarbonate and ethyl acetate, the organic layer was washed with water, dried and evaporated under reduced pressure. Purification was by chromatography eluting with 25% ethyl acetate/ isohexane . Yield 0.09g as a solid.
MS: APCI(+ve) 469 (M+1)
1H NMR: δ (DMSO-d6) 9.63(1H, d), 8.69(1H, d), 8.25(1H, d), 7.83(1H, s), 7.68(1H, s), 7.40(1H, t), 7.34-7.30(2H, m), 7.13(1H, t), 5.67(1H, d), 5.15(2H, s), 4.17-4.14(3H, m), 3.10(2H, t), 2.69-2.61(2H, m), 1.91(2H, d)
MP:159-162°C

Example 152

N-[(1R)-1-(Aminocarbonyl)-3-methylbutyl]-5-chloro-6-[4-(2-oxo-2H-3,1-benzoxazin-1 (4H)-yl)piperidin-1-yl] pyridine-3-carboxamide

[0254]

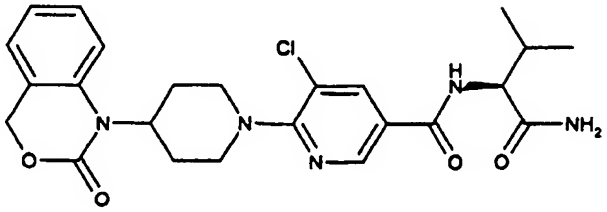


[0255] The title compound was prepared from the product of example 148 step (i) (0.15g) and (R)-leucinamide hydrochloride (0.07g) according to the method of example 115, step (i). Yield 0.05g as a solid.
MS: APCI(+ve) 500 (M+1)
1H NMR: δ (DMSO-d6) 8.68(1H, d), 8.45(1H, d), 8.27(1H, d), 7.42-7.29(4H, m), 7.12(1H, t), 6.98(1H, s), 5.15(2H, s), 4.44-4.41(1H, m), 4.15-4.07(3H, m), 3.07(2H, t), 2.68-2.64(2H, m), 1.90(2H, d), 1.70-1.54(3H, m), 0.92-0.86(6H, m)
MP:139-142°C

Example 153

N-[(1S)-1-(Aminocarbonyl)-2-methylpropyl]-5-chloro-6-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl] pyridine-3-carboxamide

[0256]

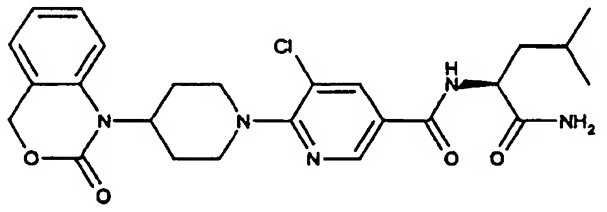


[0257] The title compound was prepared from the product of example 148 step (i) (0.15g) and (S)-valinamide hydrochloride (0.08g) according to the method of example 115, step (i). Yield 0.03g as a solid.
MS: APCI(+ve) 486 (M+1)
1H NMR: δ (DMSO-d6) 8.68(1H, t), 8.31-8.28(2H, m), 7.46-7.29(4H, m), 7.13(1H, t), 7.06(1H, s), 5.15(2H, s), 4.24-4.00 (4H, m), 3.07(2H, t), 2.73-2.61(2H, m), 2.14-2.05(1H, m), 1.90(2H, d), 0.94(3H, s), 0.92(3H, s)

Example 154

N-[(1S)-1-(Aminocarbonyl)-3-methylbutyl]-5-chloro-6-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl] pyridine-3-carboxamide

[0258]

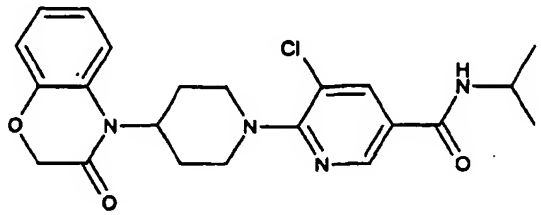


[0259] The title compound was prepared from the product of example 148 step (i) (0.15g) and (S)-leucinamide hydrochloride (0.07g) according to the method of example 115, step (i). Yield 0.04g as a solid.
MS: APCI(+ve) 500 (M+1)
1H NMR: δ (DMSO-d6) 8.68(1H, d), 8.45(1H, d), 8.27(1H, d), 7.42-7.29(4H, m), 7.13(1H, t), 6.98(1H, s), 5.15(2H, s), 4.44-4.42(1H, m), 4.15-4.04(3H, m), 3.07(2H, t), 2.68-2.64(2H, m), 1.90(2H, d), 1.66-1.54(3H, m), 0.92-0.86(6H, m)
MP:139-142°C

Example 155

5-Chloro-N-(1-methylethyl)-6-[4-(3-oxo-2,3-dihydro-4H-1,4-benzoxazin-4-yl)piperidin-1-yl]pyridine-3-carboxamide

[0260]

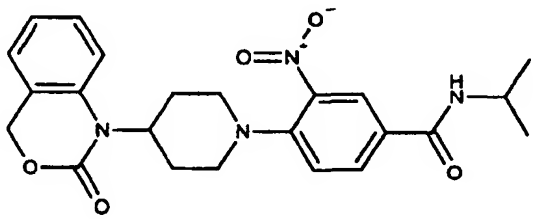


[0261] The title compound was prepared from 4-piperidin-4-yl-4H-benzo[1,4]oxazin-3-one hydrochloride (WO 9502405) (0.13g) and the product from example 117 step (i) (0.13g) according to the method of example 115 step (ii). Yield 0.04g as a solid.
MS: APCI(+ve) 429 (M+1)
1H NMR: δ (DMSO-d6) 8.64(1H, d), 8.25(1H, d), 8.18(1H, d), 7.40(1H, d), 7.12-7.03(3H m), 4.52(2H, s), 4.37-4.32(1H, m), 4.11-4.04(3H, m), 3.03(2H, t), 2.77-2.69(2H, m), 1.82(2H, d), 1.16(6H, d)
MP:85-88°C

Example 156

N-(1-Methylethyl)-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide

[0262]

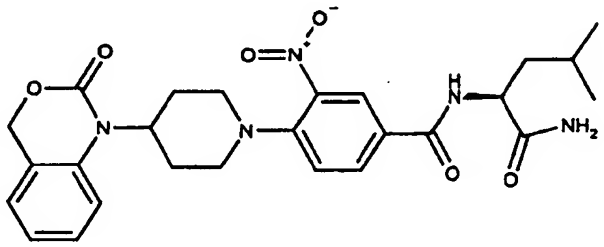


[0263] The product from example 8 step (i) (0.05g) was reacted with isopropylamine (0.02ml) using the method of example 115 step (i) in N,N-dimethylformamide (2ml). Purification was by chromatography eluting with (2:1) ethyl acetate/isohexane. Yield 0.035g as a solid.
MS: APCI(+ve) 439(M+1)
1H NMR: 8 ($CDCl_3$) 8.17(1H, m), 7.93-7.90(1H, m), 7.38-7.09(5H, m), 5.92-5.90(1H, d), 5.10(2H, s), 4.32-4.16(2H, m), 3.53-3.49(2H, m), 3.17-3.10(2H, m), 2.90-2.80(2H, m), 1.96-1.93(2H, m), 1.28-1.26(6H, d)
MP: 193-195°C

Example 157

N-[(1S)-1-(Aminocarbonyl)-2-methylbutyl]-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1 (4H)-yl)piperidin-1-yl] benzamide

[0264]

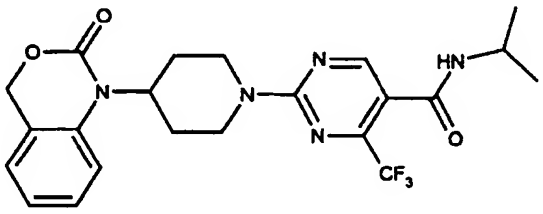


[0265] The product from example 8 step (i) (0.05g) was reacted with (S)-leucinamide hydrochloride (0.025g) using the method of example 115 step (i) in N,N-dimethylformamide (2ml). Purification was by chromatography eluting with ethyl acetate. Yield 0.025g as a solid.
MS: APCI(+ve) 510(M+1)
1H NMR: δ ($CDCl_3$) 8.29-7.09(6H, m), 6.90(1H, d), 6.22(1H, br s), 5.56(1H, br s), 5.10(2H, s), 4.73-4.11(2H, m), 3.50-2.80(6H, m), 1.97-1.70(5H, m), 1.27-1.22(1H, m), 0.99(6H, d)
MP: 146-149°C

Example 158

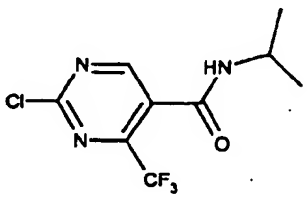
N-(1-Methylethyl)-2-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]-4-(trifluoromethyl)-5-pyrimidine-5-carboxamide.

[0266]



(i) N-(1-Methylethyl)-2-chloro-4-(trifluoromethyl)pyrimidine-5-carboxamide.

[0267]



[0268] 2-Chloro-4-(trifluoromethyl)pyrimidine-5-carbonyl chloride (1.0g) in dry N,N-dimethylformamide (5ml) was

treated with isopropylamine (0.4ml) at 0°C. The reaction mixture was stirred at 0°C for 30min, diluted with water, extracted with ethyl acetate, dried, and evaporated under reduced pressure. Purification was by chromatography eluting with 50% ethyl acetate/dichloromethane. Yield 0.74g as a solid.
MS: APCI(+ve) 268(M+1)

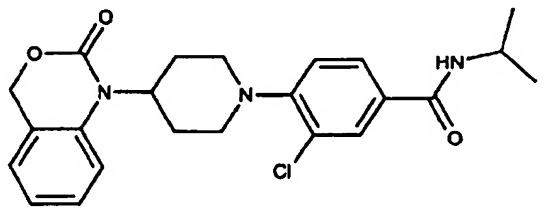
(II) N-(1-Methylethyl)-2-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl]piperidin-1-yl]-4-(trifluoromethyl)-5-pyrimidine-5-carboxamide.

[0269] The title compound was prepared from the product from step (i) (0.092g) and 1-piperidin-4-yl-1,4-dihydro-2H-3,1-benzoxazin-2-one hydrochloride (0.1g) using the method of example 115 step(ii). Purification was by chromatography eluting with (1:3) ethyl acetate/dichloromethane. Yield 0.110g as a solid.
MS: APCI(+ve) 464(M+1)
1H NMR: δ ($CDCl_3$) 8.58(1H, s), 7.38-7.08(4H, m), 5.62-5.60(1H, d), 5.10-5.05(4H, m), 4.29-4.15(2H, m), 3.06-2.62 (4H, m), 1.99-1.95(2H, d), 1.25-1.24(6H, d)
MP: 217-219°C

Example 159

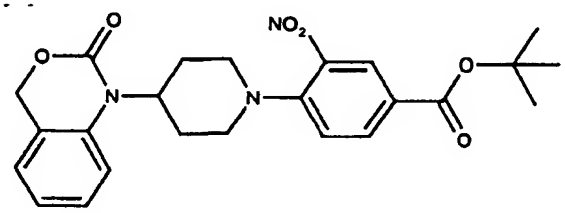
3-Chloro-N-(1-methylethyl)-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide

[0270]



(I) 1,1-Dimethylethyl 3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzoate

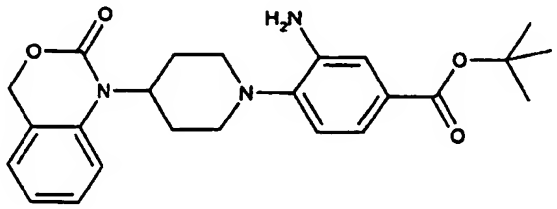
[0271]



[0272] The product was prepared from 3-nitro-4-chloro-t-butylbenzoate (0.96g) and 1-piperidin-4-yl-1,4-dihydro-2H-3,1-benzoxazin-2-one hydrochloride (1.0g) using the method of example 115 step (ii). Purification was by chromatography eluting with 50% ethyl acetate/isohexane. Yield 2.1 g as an oil.
MS: APCI(+ve) 454(M+1)

(II) 3-Amino-1,1-dimethylethyl-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzoate

[0273]



[0274] The product from step (i) (1.9g) was dissolved in glacial acetic acid (20ml) and treated with reduced iron powder (1.9g). The mixture was stirred vigorously for 2h at room temperature. The mixture was filtered through a pad of celite and the filtrate evaporated under reduced pressure. Purification was by chromatography eluting with (1:5) ethyl acetate/ dichloromethane. Yield 0.975g as a solid.
MS: APCI(+ve) 424(M+1)

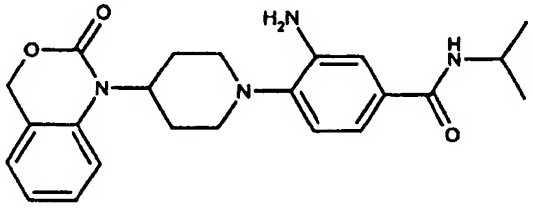
(III) 3-Chloro-N-(1-methylethyl)-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide

[0275] Product from step (ii) (0.39g) was treated with copper(II) chloride (0.148g), isoamylnitrite (0.25ml) in acetonitrile (10ml) and heated to 65°C for 4h. The reaction mixture was evaporated under reduced pressure to an oil. The oil was treated with trifluoroacetic acid/dichloromethane (1:1) and stirred at room temperature for 2h then evaporated under reduced pressure. The residue was dissolved in N,N-dimethylformamide (5ml), bromo-tris-pyyrolidino-phosphonium hexafluorophosphate (0.116g), isopropylamine (0.054ml) and N,N-diisopropylethylamine (0.06ml) were added and stirred at room temperature for 16h. The mixture was evaporated under reduced pressure. Purification was by chromatography eluting with (1:3) ethyl acetate/dichloromethane. Yield 0.017g as a solid.
MS: APCI(+ve) 428(M+1)
1H NMR: δ ($CDCl_3$) 7.76-7.06(7H, m), 5.82-5.80(1H, d), 5.10(2H, s), 4.31-4.15(2H, m), 3.65-3.62(2H, m), 2.95-2.82 (4H, m), 1.98-1.95(2H, d), 1.27-1.25(6H, d).

Example 160

3-Amino-N-(1-methylethyl)-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide

[0276]

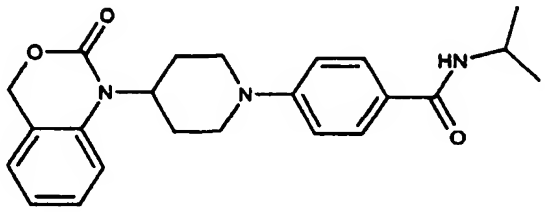


[0277] The title compound was prepared from the product of example 156 using the method described in example 159 step (ii). Yield 0.6g as a solid.
MS: APCI(+ve) 409(M+1)
1H NMR: δ (DMSO-d6) 7.89-7.86(1H, d), 7.39-6.91(7H, m), 5.15(2H, s), 4.84-4.82(2H, s), 4.08-3.99(2H, m), 3.23-3.21 (2H, m), 2.77-2.67(4H, m), 1.88-1.85(2H, m), 1.19-1.12(6H, d)

Example 161

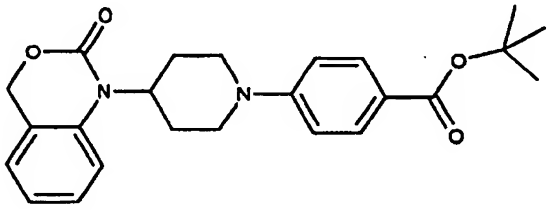
N-(1-Methylethyl)-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide

[0278]



(i) 1,1-Dimethylethyl 4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzoate

[0279]



[0280] A solution of sodium nitrite (0.11g) in water (1ml) was added to a stirred solution of the product from example 159 step (ii) (0.456g) in acetonitrile (10ml) at room temperature. After 1h a solution of iron sulphate (0.3g) in N,N-dimethylformamide (20ml) was added and the mixture stirred for a further 30min. The mixture was partitioned between ethyl acetate and water, the organics dried and evaporated under reduced pressure. Purification was by chromatography eluting with 20% ethyl acetate/isohexane. Yield 0.29g as an oil.
MS: APCI(+ve) 409(M+1)

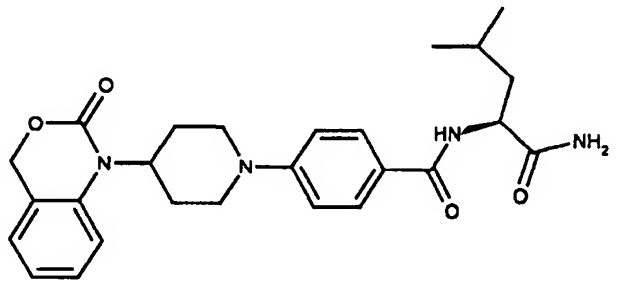
(ii) N-(1-Methylethyl)-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide

[0281] A solution of the product from step (i) (0.29g) in a mixture of trifluoroacetic acid (10ml) and dichloromethane (10ml) was stirred at room temperature for 1h. The solution was evaporated under reduced pressure, the residue dissolved in N,N-dimethylformamide then bromo-tris-pyyrolidino-phosphonium hexafluorophosphate (0.16g), isopropylamine (0.06ml) and N,N-diisopropylethylamine (0.06ml) added. The solution was stirred at room temperature for 16h then evaporated under reduced pressure. Purification was by chromatography eluting with (1:5) ethyl acetate/dichloromethane. Yield 0.01g as a solid.
MS: APCI(+ve) 394(M+1)
1H NMR: δ (DMSO-d6) 7.89-6.95(9H, m), 5.13(2H, s), 4.15-3.97(4H, m), 3.01-2.95(2H, m), 2.59-2.49(2H, m), 1.85-1.82 (2H, d), 1.13(6H, d)

Example 162

N-[(1S)-1-(Aminocarbonyl)-3-methylbutyl]-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide

[0282]

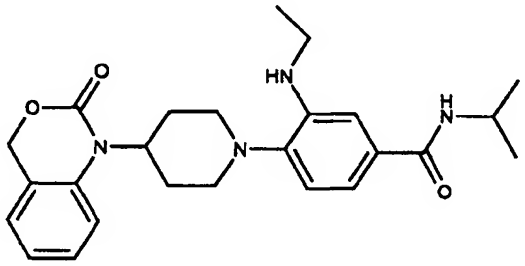


[0283] The title compound was prepared from the product of example 161 step (i) (0.06g) and (S)-leucinamide hydrochloride (0.056g) using the method of example 161 step (ii). Purification was by chromatography eluting with (5:1) ethyl acetate/dichloromethane. Yield 0.01g as a solid.
MS: APCI(+ve) 465(M+1)
1H NMR: δ (DMSO-d6) 8.04-6.92(11H, m), 5.13(2H, s), 4.44-3.99(4H, m), 3.03-2.93(2H, m), 2.60-2.49(2H, m), 1.85-1.50(5H, m), 0.88(6H, d)

Example 163

3-(Ethylamino)-N-(1-methylethyl)-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide

[0284]

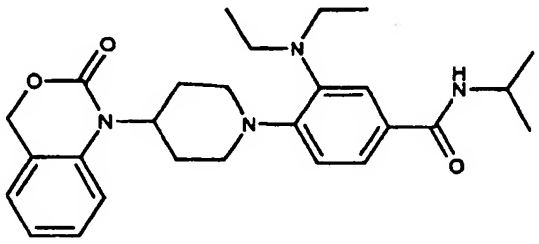


[0285] Sodium triacetoxyborohydride (0.1g) was added to a solution of the product from example 160 (0.1g), acetaldehyde (0.015ml), acetic acid (1 drop) in N,N-dimethylformamide (10ml). The reaction mixture was stirred at room temperature for 16h. The mixture was diluted with water, extracted with ethyl acetate, dried, and evaporated under reduced pressure. Yield 0.035g.
MS: APCI(+ve) 437(M+1)
1H NMR: δ (DMSO-d6) 7.96-6.98(8H, m), 5.15(2H, s), 4.73-4.70(1H, t), 4.13-3.99(2H, m), 3.25-3.14(4H, m), 2.81-2.64 (4H, m), 1.90-1.88(2H, m), 1.26-1.14(9H, m)

Example 164

3-(Diethylamino)-N-(1-methylethyl)-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide

[0286]

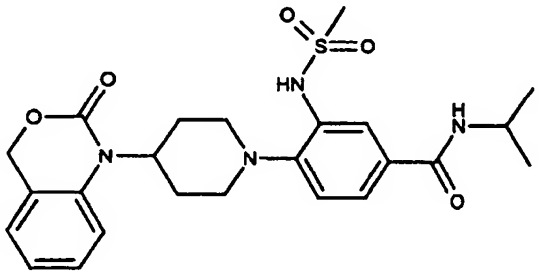


[0287] The title compound was obtained from the reaction mixture in example 163. Yield 0.052g.
MS: APCI(+ve) 465(M+1)
1H NMR: δ (DMSO-d6) 7.97-6.90(8H, m), 5.15(2H, s), 4.11-3.99(2H, m), 3.86-3.83(2H, m), 3.31-3.18(4H, m), 2.72-2.63 (4H, m), 1.86(2H, m), 1.19-1.14(6H, d), 1.03-0.95(6H, m)

Example 165

N-(1-Methylethyl)-3-[(methylsulfonyl)amino]-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide

[0288]

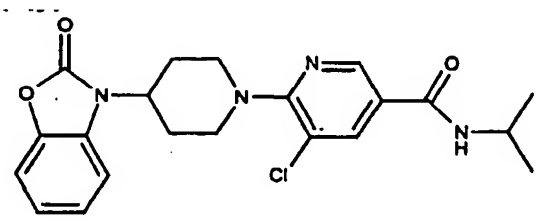


[0289] The title compound was prepared from the product of example 160 (0.1g) and methanesulphonylchloride (0.02ml) in dichloromethane (10ml) at 0°C in the presence of 2,6-lutidine (0.085ml). The reaction mixture was stirred at room temperature for 16h. The mixture was evaporated, dissolved in ethyl acetate, washed with water, dried, and evaporated under reduced pressure. Purification was by chromatography eluting with (3:1) ethyl acetate/isohexane. Yield 0.066g as a solid.
MS: APCI(+ve) 487(M+1)
1H NMR: δ (DMSO-d6) 8.63(1H,s), 8.16-8.13(1H, d), 7.76-7.10(7H, m), 5.16(2H, s), 4.14-3.99(2H, m), 3.27-3.23(2H, m), 3.19(3H, s), 2.93-2.70(4H, m), 1.89-1.86(2H, m), 1.17-1.14(6H, d)

Example 166

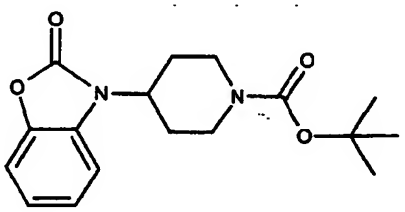
5-Chloro-N-(1-methylethyl)-6-[4-(2-oxo-1,3-benzoxazol-3(2H)-yl)piperidin-1-yl]pyridine-3-carboxamide

[0290]



(i) 1,1-Dimethylethyl 4-(2-oxo-1,3-benzoxazol-3(2H)-yl)piperidine-1-carboxylate

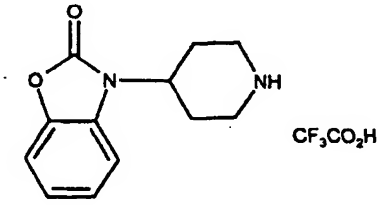
[0291]



[0292] 2-Benzoxazolinone (1g) was added to a cooled solution of triphenylphoshine (2.13g) and diethylazodicarboxylate (1.28ml) in dry tetrahydrofuran (20ml). After 10min at 0°C, N-(t-butoxy)-4-hydroxypiperidine (1.63g) (Tetrahedron Letters, 1996, 6439-6442) was added portionwise. The reaction mixture was stirred at room temperature for 16h. The solution was diluted with water, extracted with ethyl acetate, dried and evaporated under reduced pressure. Purification was by chromatography eluting with (1:2) diethylether/isohexane. Yield 0.5g as an oil.
MS: APCI(+ve) 219(M+1) -BOC

(ii) 3-Piperidin-4-yl-1,3-benzoxazol-2(3H)-one, trifluoroacetic acid salt

[0293]



[0294] The product from step (i) (0.5g) was stirred at room temperature in (1:1) trifluoroacetic acid/dichloromethane (10ml) for 30min. The reaction mixture was evaporated under reduced pressure to give an oil. Used crude.
MS: APCI(+ve) 219(M+1)

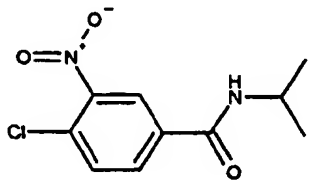
(iii) 5-Chloro-N-(1-methylethyl)-6-[4-(2-oxo-1,3-benzoxazol-3(2H)-yl)piperidin-1-yl]pyridine-3-carboxamide

[0295] The title compound was prepared from the product of example 117 step(i) (0.53g) and the product from step (ii) by the method described in example 115 step (ii). Purification was by chromatography eluting with 50% ethyl acetate/ isohexane. Yield 0.28g as a solid.
MS: APCI(+ve) 415(M+1)
1H NMR: δ (DMSO-d6) 8.66-7.12(7H, m), 4.44-4.38(1H, m), 4.10-4.05(3H, m), 3.09-3.03(2H, t), 2.45-2.35(2H, m), 1.95-1.92(2H, m), 1.17-1.15(6H, d)
MP: 162-168°C

Examples 167-169

(i) 4-Chloro-N-(1-methylethyl)-3-nitrobenzamide

[0296]



[0297] Isopropylamine (1.28ml) was added dropwise to a stirred solution of 4-chloro-3-nitrobenzoylchloride (3.0g) and triethylamine (2.8ml) in dichloromethane (30ml) at room temperature. After 2h the mixture was partitioned between ethyl acetate and water, the organics dried and evaporated under reduced pressure. Yield 2.87g.
1H NMR: δ (DMSO-d6) 8.58(1H, d), 8.51(1H, d), 8.15(1H, dd), 7.89(1H, d), 4.14-4.06(1H, m), 1.18(6H, d)

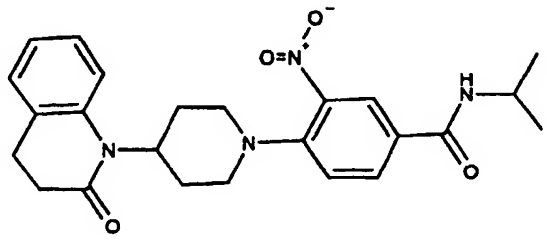
(ii) Examples 167-169

[0298] A solution of the product from step (i) (Img), N,N-diisopropylethylamine (3 equiv.), the appropriate amine (1.5 equiv.) in 1-methyl-2-pyrrolidinone (0.16ml) were heated at 65°C for 30h. The reaction mixture was evaporated to dryness and the residue dissolved in dimethylsulphoxide (0.4ml).

Example 167

N-(1-Methylethyl)-3-nitro-4-[4-(2-oxo-3,4-dihydroquinolin-1(2H)-yl)piperidin-1-yl]benzamide

[0299]

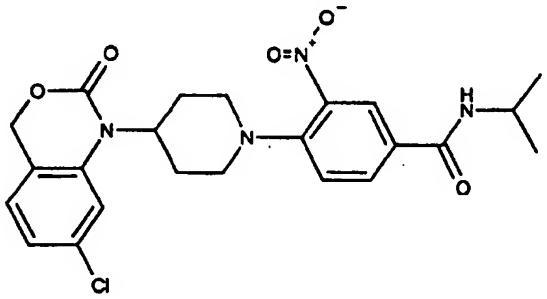


MS: APCI(+ve) 436(M+1)

Example 168

4-[4-(7-Chloro-2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]-N-(1-methylethyl)-3-nitrobenzamide

[0300]

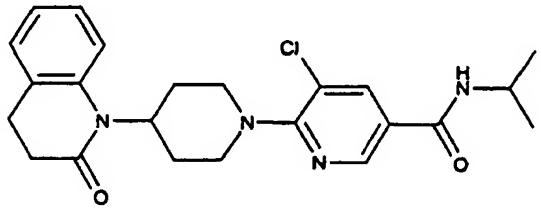


MS: APCI(+ve) 472(M+1)

Example 169

5-Chloro-N-(1-methylethyl)-6-[4-(2-oxo-3,4-dihydroquinolin-1(2H)-yl)piperidin-1-yl]pyridine-3-carboxamide

[0301]

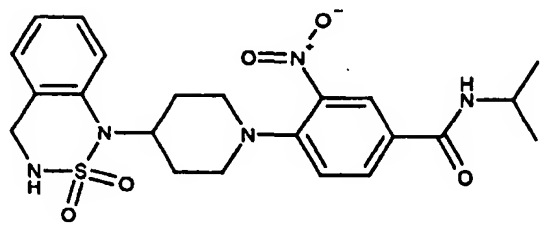


[0302] The title compound was prepared from 1-piperidin-4-yl-3,4-dihydro-1H-quinolin-2-one (0.03g) and the product from example 117 step (i) (0.03g) by the method of example 115 step (ii). Purification was by chromatography eluting with 50% ethyl acetate/l-hexane. Yield 0.017g as a white solid.
MS: APCI(+ve) 427 (M+1)
1H NMR: δ (DMSO-d6) 8.49(1H, d), 7.98(1H, d), 7.20(3H, m), 7.02(1H, t), 5.83(1H, d), 4.50(1H, m), 4.20(3H, m), 2.98 (2H, t), 2.80(4H, m), 2.60(2H, t) 1.83(2H, m), 1.25(6H, d)

Example 170

4-[4-(2,2-Dioxido-3,4-dihydro-1H-2,1,3-benzothiadiazin-1-yl)piperidin-1-yl]-N-(1-methylethyl)-3-nitrobenzamide

[0303]

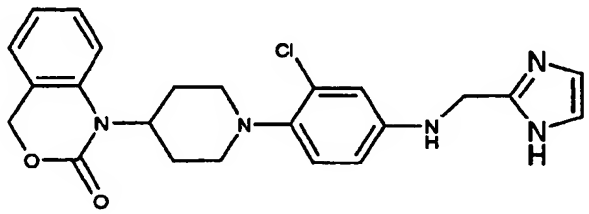


[0304] The title compound was prepared from 1-Piperidin-4-yl-3,4-dihydro-1H-benzo[1,2,6]thiadiazine 2,2-dioxide (Chem. Pharm. Bull. (1985), 33(3), 1104-15) (0.05g) and the product from example 167 step (i) (0.05g) by the method of example 115 step (ii). Purification was by chromatography eluting with ethyl acetate. Yield 0.03g as a white solid.
MS: APCI(+ve) 474 (M+1)
1H NMR: δ (DMSO-d6) 8.32 (2H, m), 8.00 (1H, d), 7.72 (1H, t), 7.30 (2H, m), 7.20 (2H, d), 7.10 (1H, t), 4.41 (2H, d), 4.10 (3H, m), 3.40 (1H, m), 3.04 (2H, t), 2.00 (4H, m), 1.15 (6H,d).

Example 171

1-(1-{2-Chloro-4-[(1H-imidazol-2-ylmethyl)amino]phenyl}piperidin-4-yl)-1,4-dihydro-2H-3,1-benzoxazin-2-one

[0305]



[0306] The product of example 120 step (ii) (0.25g) was dissolved in 1-methyl-2-pyrrolidinone (6ml) and this solution was treated with 2-imidazolecarboxaldehyde (0.1 g) followed by acetic acid (0.13g) and then sodium triacetoxyborohydride (0.37g). the reaction mixture was stirred at room temperature for three days. At the end of this time the mixture was poured in to excess aqueous dilute hydrochloric acid, this solution was allowed to stand for 10 minutes before being basified by addition of excess aqueous sodium bicarbonate. The mixture was extracted with ethyl acetate, the organic layer was washed with water, dried and evaporated under reduced pressure. Purification was by chromatography eluting with methanol/chloroform (7/93). Yield 0.05g as a solid.
MS: APCI (=ve) 438 (M+1)
1H NMR: δ (DMSO-d6) 11.84 (1H, s), 7.41 (1H, t), 7.31 - 7.27(2H, m), 7.11(1H, t), 6.97(1H, d), 6.92(2H, s), 6.73(1H, d), 6.57(1H, q), 6.06(1H, t), 5.14(2H, s), 4.19(2H, d), 3.98 - 3.93(1H, m), 3.15(2H, d), 2.78 - 2.63(4H, m) 1.83(2H, d)
MP:222-224°C

Pharmacological Analysis

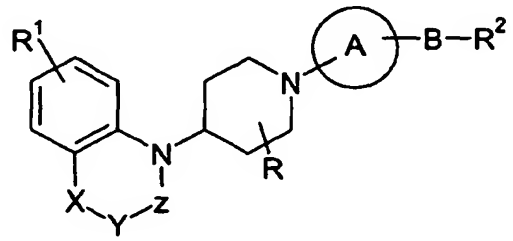
[0307] Certain compounds such as benzoylbenzoyl adenosine triphosphate (bbATP) are known to be agonists of the $P2X_7$ receptor, effecting the formation of pores in the plasma membrane (Drug Development Research (1996), 37 (3), p.126). Consequently, when the receptor is activated using bbATP in the presence of ethidium bromide (a fluorescent DNA probe), an increase in the fluorescence of intracellular DNA-bound ethidium bromide is observed. The in-

crease in fluorescence can be used as a measure of $P2X_7$ receptor activation and therefore to quantify the effect of a compound on the $P2X_7$ receptor.

[0308] In this manner, each of the title compounds was tested for antagonist activity at the $P2X_7$ receptor. Thus, the test was performed in 96-well flat bottomed microtitre plates, the wells being filled with 100 µl of test solution comprising 80 µl of a suspension of THP-1 cells (2.5 x 10^6 cells/ml) containing 10^{-4}M ethidium bromide, 10 µl of a high potassium buffer solution containing 10^{-5}M bbATP, and 10 µl of the high potassium buffer solution containing 1 x 10^{-4}M test compound (in 10% v/v DMSO). The plate was covered with a plastic lid and incubated at 37°C for one hour. The plate was then read in a Spectromax Gemini Fluorescent plate reader excitation 525 nm, emission 610 nm, slit widths: Ex 15 nm, Em 20 nm. For the purposes of comparison, bbATP (a $P2X_7$ receptor agonist) and N-(5-methoxy-2-methylphenyl)-tricyclo[3.3.1.$1^{3,7}$]decane-1-acetamide (WO99/29660, a $P2X_7$ receptor antagonist) were used separately in the test as controls. From the readings obtained, a pIC_{50} figure was calculated for each test compound, this figure being the negative logarithm of the concentration of test compound necessary to reduce the bbATP agonist activity by 50%. The pIC_{50} was then corrected using a modified Cheng Prusoff calculation based on agonist A_{50} (Trends in Pharmacological Sciences (1993), 14(4), 110-2). Each of the compounds of the Examples demonstrated antagonist activity, having a pIC_{50} figure > 5.00.

Claims

1. A compound of formula (I):



(I)

where
A is phenyl or a 5- or 6-membered heterocyclic ring containing one or two heteroatoms selected from O, N or S; and optionally substituted by C_{1-6}alkyl, halogen, nitro, amino, C_1-C_6alkylamino, CF_3, SO_2Me, $NHSO_2Me$ or cyano;
B is C=O, NH or SO_2;
X is C=O, CH(Me), O or $(CH_2)p$ where p is 0 or 1;
Y is O, CH_2, NH or S;
Z is C=O or SO_2, provided that when Z is C=O, then Y is O, CH_2 or S;
R is hydrogen or C_{1-6}alkyl;
R^1 is hydrogen, halogen;
R^2 is phenyl optionally substituted by CO_2H, CO_2-C_1-C_6alkyl, $CONH_2$ or R^2 is OH, NHR^3, $NHCH(R^4)(CHR^5)_nR^6$, NH-R^7-R^8, SO_2NHC_1-C_6alkyl, $NHCOC_1$-C_6alkyl, $NHSO_2C_1$-C_6alkyl, morpholine, NR^9R^{10}, piperazine substituted by phenyl, C_1-C_6alkoxyphenyl, pyridyl or fluorophenyl;
n is 0, 1 or 2;
R^3 is hydrogen, a bi- or tricyclic saturated ring system optionally containing a nitrogen atom, piperidinyl, C_1-C_6alkylpyrrolidine, ethynylcyclohexyl, a 5-membered aromatic ring containing 2 or 3 heteroatoms, C_{4-6} cycloalkyl optionally substituted by C_1-C_6alkyl, cyano or hydroxy, or C_{1-8} alkyl optionally containing an oxygen atom in the alkyl chain and being optionally substituted by one or more substituents selected from ethynyl, cyano, fluoro, di-C_1-C_6alkylamino, hydroxy, thioC_1-C_6alkyl, CO_2R^{11} or $CONH_2$;
R^4 is hydrogen or C_1-C_6alkyl optionally substituted by hydroxy or C_1-C_6alkoxy;
R^5 is hydrogen or hydroxy;
R^6 is CO_2R^{11}, $NHCO_2R^{12}$, $CONH_2$ or a 5 or 6-membered saturated ring containing an oxygen atom, a 5-membered heterocyclic ring containing one or two heteroatoms selected from O, N or S, or phenyl optionally substituted by one or more groups selected from C_1-C_6alkyl, hydroxy, amino, C_1-C_6alkoxy, or nitro;
R^6 is C_1-C_6alkyl;

R^7 is a cyclopentane ring;
R^8 is phenyl;
$R^9$and R^{10} are independently hydrogen, benzyl, alkenyl, cycloalkyl, C_1-C_6alkyl optionally substituted by hydroxy, C_1-C_6alkoxy, cyano, di-C_1-C_6alkylamino, phenyl, pyridyl or CO_2R^{11} or R^9 and R^{10} together form a 5- to 7-membered saturated or partially saturated ring optionally containing a further heteroatom and optionally substituted by one or more groups selected from C_1-C_6alkyl (optionally containing an oxygen atom in the chain and optionally substituted by hydroxy), COC_1-C_6alkyl, CO_2R^{11}, $COR^{13}R^{14}$, CHO or piperidine,
R^{11} is hydrogen or C_1-C_6alkyl;
R^{12} is C_1-C_6alkyl; and
R^{13} and R^{14} are independently hydrogen or C_1-C_6alkyl,
or a pharmaceutically acceptable salt or solvate thereof.

2. A compound according to claim 1 in which A is phenyl optionally substituted by $C_{1\text{-}6}$alkyl, halogen, nitro, amino, C_1-C_6alkylamino, CF_3, SO_2Me, $NHSO_2Me$ or cyano.

3. A compound according to claim 1or 2 in which B is C=O.

4. A compound according to any one of claims 1 to 3 in which X is CH_2, Y is O and Z is C=O.

5. A compound according to any one of claims 1 to 4 in which R is hydrogen.

6. A compound according to any one of claims 1 to 5 in which R^1 is hydrogen.

7. A compound according to any one of claims 1 to 6 in which R^2 is NR^9R^{10} where one of R^9 or R^{10} is hydrogen and the other is C_1-C_6alkyl.

8. A compound according to claim 1 which is:

2-({3-Nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]phenyl}carbonyl)benzoic acid,
1-{1-[2-Nitro-4-(phenylcarbonyl)phenyl]piperidin-4-yl}-1,4-dihydro-2H-3,1-benzoxazin-2-one,
Methyl 2-({3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]phenyl }carbonyl)benzoate,
2-({3-Nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]phenyl } carbonyl)benzamide,
Methyl 2-({3-nitro-4-[4-(2-oxo-3,4-dihydroquinolin-1(2H)-yl)piperidin-1-yl]phenyl } carbonyl)benzoate,
2-({3-Nitro-4-[4-(2-oxo-3,4-dihydroquinolin-1(2H)-yl)piperidin-1-yl]phenyl}carbonyl)benzoic acid,
Methyl 2-({4-[4-(7-chloro-2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]-3-nitrophenyl }carbonyl)benzoate,
N-(1,1-Dimethylethyl)-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide,
N-[(1R)-2-Hydroxy-1-(phenylmethyl)ethyl]-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl] benzamide,
Methyl 2-[({3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]phenyl}carbonyl)amino]propanoate,
3-Nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]-N-(tetrahydrofuran-2-ylmethyl)benzamide,
N-[2-(4-Aminophenyl)ethyl]-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide,
3-Nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]-N-(2,2,2-trifluoroethyl)benzamide,
Ethyl (2S)-3-methyl-2-[({3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]phenyl} carbonyl)amino]butanoate,
Methyl 3-hydroxy-2-[({3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]phenyl} carbonyl)amino] propanoate,
N-[2-(3,4-Dihydroxyphenyl)ethyl]-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide,
3-Nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]-N-(2-phenylethyl)benzamide,
N-[(4-Aminophenyl)methyl]-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide,
3-Nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]-N-(2-thien-2-ylethyl)benzamide,
N-[3-(Dimethylamino)-2,2-dimethylpropyl]-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl] benzamide,
N-{[2,4-Bis(methyloxy)phenyl]methyl}-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide,
N-Bicyclo[2.2.1]hept-2-yl-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide,
N-(2-Fluoroethyl)-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide,

3-Nitro-N-[(3-nitrophenyl)methyl]-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide,
N-[(1S,2R)-2-Hydroxy-1-methyl-2-phenylethyl]-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide,
3-Nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]-N-{[3,4,5-tris(methyloxy)phenyl]methyl}benzamide,
3-Nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]-N-(2-phenylcyclopropyl)benzamide,
N-[2-Hydroxy-1-(hydroxymethyl)-1-methylethyl]-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide,
N-(1-Azabicyclo[2.2.2]oct-3-yl)-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide,
3-Nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]-N-(2-piperidin-1-ylethyl)benzamide,
N-(1,3-Dimethylbutyl)-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide,
N-(1-Methylbutyl)-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide,
N-(1-Methylhexyl)-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide,
N-(3-Methylbutyl)-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide,
N-[(2-Aminophenyl)methyl]-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide,
N-[2-Hydroxy-1-(hydroxymethyl)ethyl]-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide,
N-[2-(Ethylthio)ethyl]-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide,
N-[(1S)-1-(Hydroxymethyl)-2,2-dimethylpropyl]-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide,
N-(4-Methylcyclohexyl)-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide,
N- {2-Hydroxy-1-[(methyloxy)methyl]-2-phenylethyl}-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide,
N-Ethyl-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide,
N-Cyclopropyl-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide,
3-Nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]-N-(phenylmethyl)benzamide,
N-(1-Methylpropyl)-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide,
1,1-Dimethylethyl 2-[({3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]phenyl } carbonyl)amino] ethylcarbamate,
N-[2-(3,4-Dihydroxyphenyl)ethyl]-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide,
N- { [4-(Methyloxy)phenyl]methyl}-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide,
N-[2-(1H-Imidazol-4-yl)ethyl]-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide,
N-[(1S)-1-(Hydroxymethyl)propyl]-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin- 1-yl]benzamide,
3-Nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]-N-[1-(phenylmethyl)piperidin-4-yl]benzamide,
N-[(1R)-1-(Hydroxymethyl)propyl]-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide,
N-(4-Hydroxybutyl)-3 -nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide,
3-Nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]-N-tricyclo[3.3.1.1~3,7~]dec-1-ylbenzamide,
N-[(1S,2S)-2-Hydroxycyclohexyl]-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide,
N-(2-Hydroxy-1-methylethyl)-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide,
N-{2-[(2-Hydroxyethyl)oxy]ethyl}-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide,
N-[1-(Hydroxymethyl)butyl]-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide,
N-(2-Amino-2-oxoethyl)-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide,
N-[1-(4-Fluorophenyl)ethyl]-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide,
3-Nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]-N-(3-phenylpropyl)benzamide,
N-[(1S,2R)-2-Hydroxycyclohexyl]-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide,
Ethyl 3-hydroxy-2-[({3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]phenyl} carbonyl)amino] propanoate,
N-[(1R,2S)-2-Hydroxy-1-methyl-2-phenylethyl]-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide,
1-{1-[4-(Morpholin-4-ylcarbonyl)-2-nitrophenyl]piperidin-4-yl}-1,4-dihydro-2H-3,1-benzoxazin-2-one,
N,N-Dimethyl-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide,
N,N-Bis(2-hydroxyethyl)-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide,
N-(2-Hydroxyethyl)-N-methyl-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide,
N-(2-Hydroxyethyl)-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]-N-(phenylmethyl)benzamide,
1-(1-{2-Nitro-4-[(4-phenylpiperazin-1-yl)carbonyl]phenyl}piperidin-4-yl)-1,4-dihydro-2H-3,1-benzoxazin-2-one,
N-[(1S,2R)-2-hydroxy-1-methyl-2-phenylethyl]-N-methyl-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)pip-

eridin-1-yl]benzamide,
N-Ethyl-N-(2-hydroxyethyl)-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide,
1-[1-(4-{[4-(4-Fluorophenyl)piperazin-1-yl]carbonyl}-2-nitrophenyl)piperidin-4-yl]-1,4-dihydro-2H-3,1-benzoxazin-2-one,
1-{1-[4-(Azepan-1-ylcarbonyl)-2-nitrophenyl]piperidin-4-yl}-1,4-dihydro-2H-3,1-benzoxazin-2-one,
N,N-Diethyl-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide,
N-[2-(Dimethylamino)ethyl]-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]-N-(phenylmethyl)benzamide,
N-Ethyl-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]-N-(phenylmethyl)benzamide,
N-Butyl-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]-N-(phenylmethyl)benzamide,
1-{1-[2-Nitro-4-(piperidin-1-ylcarbonyl)phenyl]piperidin-4-yl}-1,4-dihydro-2H-3,1-benzoxazin-2-one,
Ethyl [({3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]phenyl }carbonyl)(phenylmethyl)amino]acetate,
N-(2-Hydroxyethyl)-N-(1-methylethyl)-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide,
1-(1-{2-Nitro-4-[(4-pyridin-2-ylpiperazin-1-yl)carbonyl]phenyl}piperidin-4-yl)-1,4-dihydro-2H-3,1-benzoxazin-2-one,
1-{1-[2-Nitro-4-{pyrrolidin-1-ylcarbonyl)phenyl]piperidin-4-yl}-1,4-dihydro-2H-3,1-benzoxazin-2-one,
N-(2-Hydroxyethyl)-3-nitro-4- [4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]-N-pentylbenzamide,
N-[2-(Diethylamino)ethyl]-N-ethyl-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide,
N-Ethyl-N-methyl-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide,
(2S)-1-({3-Nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]phenyl}carbonyl)pyrrolidine-2-carboxamide,
N-(2-Cyanoethyl)-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]-N-(phenylmethyl)benzamide,
1-(1-{4-[(3,5-Dimethylpiperidin-1-yl)carbonyl]-2-nitrophenyl}piperidin-4-yl)-1,4-dihydro-2H-3,1-benzoxazin-2-one,
1-[1-(4-{[(2R,6S)-2,6-Dimethylmorpholin-4-yl]carbonyl}-2-nitrophenyl)piperidin-4-yl]-1,4-dihydro-2H-3,1-benzoxazin-2-one,
1-{1-[4-({4-[2-(Methyloxy)phenyl]piperazin-1-yl}carbonyl)-2-nitrophenyl]piperidin-4-yl}-1,4-dihydro-2H-3,1-benzoxazin-2-one,
1-{1-[2-Nitro-4-(thiomorpholin-4-ylcarbonyl)phenyl]piperidin-4-yl}-1,4-dihydro-2H-3,1-benzoxazin-2-one,
1-(1-{4-[(4-{2-[(2-Hydroxyethyl)oxy]ethyl}piperazin-1-yl)carbonyl]-2-nitrophenyl}piperidin-4-yl)-1,4-dihydro-2H-3,1-benzoxazin-2-one,
N-Ethyl-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]-N-(pyridin-4-ylmethyl)benzamide,
N-Methyl-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]-N-prop-2-ynylbenzamide,
1-(1-{4-[(4-Acetylpiperazin-1-yl)carbonyl]-2-nitrophenyl}piperidin-4-yl)-1,4-dihydro-2H-3,1-benzoxazin-2-one,
1-[1-(4-{[2-(Hydroxymethyl)piperidin-1-yl]carbonyl}-2-nitrophenyl)piperidin-4-yl]-1,4-dihydro-2H-3,1-benzoxazin-2-one,
4-({3-Nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]phenyl}carbonyl)piperazine-1-carbaldehyde,
N-Methyl-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]-N-(phenylmethyl)benzamide,
Ethyl 4-({3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]phenyl}carbonyl)piperazine-1-carboxylate,
Ethyl 1-({3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]phenyl} carbonyl)piperidine-4-carboxylate,
1-({3-Nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]phenyl }carbonyl)piperidine-3-carboxamide,
1-(1-{4-[(4-Methylpiperazin-1-yl)carbonyl]-2-nitrophenyl}piperidin-4-yl)-1,4-dihydro-2H-3,1-benzoxazin-2-one,
1-{ 1-[4-(2,5-Dihydro-1H-pyrrol-1-ylcarbonyl)-2-nitrophenyl]piperidin-4-yl}-1,4-dihydro-2H-3,1-benzoxazin-2-one,
N-Ethyl-N-(2-methylprop-2-enyl)-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin- 1-yl]benzamide,
N,N-Bis(cyanomethyl)-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide,
N-Butyl-N-(cyanomethyl)-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide,
N,N-Bis(2-hydroxypropyl)-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide,
1-(1-{4-[(4-Hydroxypiperidin-1-yl)carbonyl]-2-nitrophenyl}piperidin-4-yl)-1,4-dihydro-2H-3,1-benzoxazin-

2-one,
1-(1-{4-[(2,5-Dimethyl-2,5-dihydro-1H-pyrrol-1-yl)carbonyl]-2-nitrophenyl} piperidin-4-yl)-1,4-dihydro-2H-3,1-benzoxazin-2-one,
N-Methyl-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]-N-propylbenzamide,
N-(2-Amino-2-oxoethyl)-N-methyl-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin- 1-yl]benzamide,
N,N-Diethyl-1-({3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]phenyl}carbonyl)piperidine-3-carboxamide,
N-Cyclohexyl-N-methyl-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide,
N-[2-(Methyloxy)ethyl]-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide,
N-(1-Methylethyl)-6-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]pyridine-3-carboxamide,
5-Chloro-N-(1-methylethyl)-6-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]pyridine-3-carboxamide,
N-(1-Methylethyl)-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzenesulfonamide,
1-[1-(4-Amino-2-chlorophenyl)piperidin-4-yl]-1,4-dihydro-2H-3,1-benzoxazin-2-one,
3-Cyano-N-(1-methylethyl)-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide,
N-{3-Chloro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]phenyl}-2-methylpropanamide,
N-{3-Chloro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]phenyl}propane-2-sulfonamide,
N-{3-Chloro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]phenyl}-1-cyanocyclopropanecarboxamide,
(2S)-N-{3-Chloro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]phenyl}-1-methylpyrrolidine-2-carboxamide,
5-Chloro-N-(1-methylethyl)-6-[4-(4-methyl-2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1 -yl]pyridine-3-carboxamide,
±-5-Chloro-N-(1-methylethyl)-6-[(cis)-3-methyl-4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]pyridine-3-carboxamide,
±-5-Chloro-N-(1-methylethyl)-6-[(trans)-3 -methyl-4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]pyridine-3-carboxamide,
2-[4-(2-Oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]-N-(1,3,4-thiadiazol-2-yl)-4-(trifluoromethyl)pyrimidine-5-carboxamide,
2-[4-(2-Oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]-N-(1H-1,2,4-triazol-3-yl)-4-(trifluoromethyl)pyrimidine-5-carboxamide,
2-[4-(2-Oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]-N-(1H-pyrazol-3-yl)-4-(trifluoromethyl)pyrimidine-5-carboxamide,
N-(4-Hydroxycyclohexyl)-2-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]-4-(trifluoromethyl)pyrimidine-5-carboxamide,
N-[1-(Hydroxymethyl)propyl]-2-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]-4-(trifluoromethyl)pyrimidine-5-carboxamide,
N-(3-Hydroxy-2,2-dimethylpropyl)-2-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]-4-(trifluoromethyl) pyrimidine-5-carboxamide,
2-[4-(2-Oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]-N-(tetrahydrofuran-2-ylmethyl)-4-(trifluoromethyl)pyrimidine-5-carboxamide,
N-Cyclobutyl-2-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]-4-(trifluoromethyl)pyrimidine-5-carboxamide,
N-Cyclopentyl-2-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]-4-(trifluoromethyl)pyrimidine-5-carboxamide,
N-[2-(1H-Imidazol-4-yl)ethyl]-2-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]-4-(trifluoromethyl)pyrimidine-5-carboxamide,
N-(1-Ethynylcyclohexyl)-2-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]-4-(trifluoromethyl)pyrimidine-5-carboxamide,
N-[(1R)-1(Hydroxymethyl)-2-methylpropyl]-2-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]-4-(trifluoromethyl)pyrimidine-5-carboxamide,
N-(2-Hydroxy-1,1-dimethylethyl)-2-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]-4-(trifluoromethyl) pyrimidine-5-carboxamide,
N-(1,1-Diethylprop-2-ynyl)-2-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]-4-(trifluoromethyl)pyrimidine-5-carboxamide,
N-(2-Hydroxy-1-methylethyl)-2-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]-4-(trifluoromethyl)pyrimidine-5-carboxamide,
N-[1-Methyl-2-(methyloxy)ethyl]-2-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]-4-(trifluoromethyl) pyrimidine-5-carboxamide,

N-(1-Methylethyl)-2-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]pyrimidine-5-carboxamide,
N-(1-Methylethyl)-2-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]-1,3-thiazole-4-carboxamide,
N-(1-Methylethyl)-3-(methylsulfonyl)-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide,
N-[(1R)-1-(Aminocarbonyl)-2-methylpropyl]-5-chloro-6-[4-(2-oxo-2H-3,1-benzoxazin-1 (4H)-yl)piperidin-1-yl] pyridine-3-carboxamide,
5-Chloro-N-(2-hydroxy-1-methylethyl)-6-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]pyridine-3-carboxamide,
5-Chloro-N-(1,1-dimethylprop-2-ynyl)-6-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]pyridine-3-carboxamide,
N-(2-Amino-1-cyano-2-oxoethyl)-5-chloro-6-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]pyridine-3-carboxamide,
N-[(1R)-1-(Aminocarbonyl)-3-methylbutyl]-5-chloro-6-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl] pyridine-3-carboxamide,
N-[(1S)-1-(Aminocarbonyl)-2-methylpropyl]-5-chloro-6-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl] pyridine-3-carboxamide,
N-[(1S)-1-(Aminocarbonyl)-3-methylbutyl]-5-chloro-6-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl] pyridine-3-carboxamide,
5-Chloro-N-(1-methylethyl)-6-[4-(3-oxo-2,3-dihydro-4H-1,4-benzoxazin-4-yl)piperidin-1-yl]pyridine-3-carboxamide,
N-(1-Methylethyl)-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide,
N-[(1S)-1-(Aminocarbonyl)-2-methylbutyl]-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl] benzamide,
N-(1-Methylethyl)-2-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]-4-(trifluoromethyl)-5-pyrimidine-5-carboxamide,
3-Chloro-N-(1-methylethyl)-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide,
3-Amino-N-(1-methylethyl)-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide,
N-(1-Methylethyl)-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide,
N-[(1S)-1-(Aminocarbonyl)-3-methylbutyl]-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide,
3-(Ethylamino)-N-(1-methylethyl)-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide,
3-(Diethylamino)-N-(1-methylethyl)-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide,
N-(1-Methylethyl)-3-[(methylsulfonyl)amino]-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamide,
5-Chloro-N-(1-methylethyl)-6-[4-(2-oxo-1,3-benzoxazol-3(2H)-yl)piperidin-1-yl]pyridine-3-carboxamide,
N-(1-Methylethyl)-3-nitro-4-[4-(2-oxo-3,4-dihydroquinolin-1(2H)-yl)piperidin-1-yl]benzamide,
4-[4-(7-Chloro-2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]-N-(1-methylethyl)-3-nitrobenzamide,
5-Chloro-N-(1-methylethyl)-6-[4-(2-oxo-3,4-dihydroquinolin-1(2H)-yl)piperidin-1-yl]pyridine-3-carboxamide,
4-[4-(2,2-Dioxido-3,4-dihydro-1H-2,1,3-benzothiadiazin-1-yl)piperidin-1-yl]-N-(1-methylethyl)-3-nitrobenzamide,

or a pharmaceutically acceptable salt or solvate thereof.

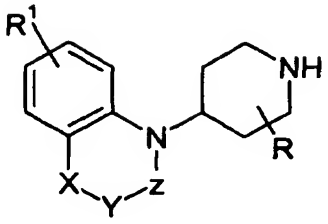
9. A pharmaceutical composition comprising a compound according to any one of claims 1 to 8 in combination with a pharmaceutically acceptable diluent, adjuvent or carrier.

10. A compound according to any one of claims 1 to 8 for use in therapy.

11. A compound according to any one of claims 1 to 8 for use in the treatment of rheumatoid arthritis.

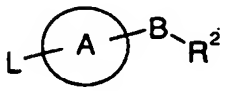
12. Use of a compound according to any one of claims 1 to 8 in the manufacture of a medicament for use in therapy.

13. A process for the preparation of a compound of formula (I) according to claim 1 which comprises reaction of a compound of formula (II):



(II)

where R, R^1, X, Y and Z are as defined in formula (I) or a protected derivative thereof, with a compound of formula (III):



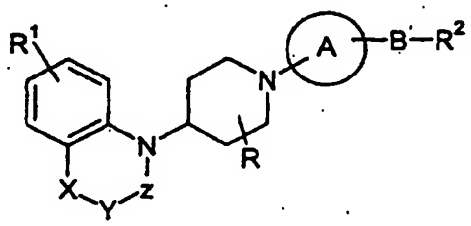
(III)

where B and R^2 are as defined in formula (I) or a protected derivative thereof, and L is a leaving group, and optionally thereafter in any order:

- converting one or more functional groups into further functional groups
- removing any protecting groups
- forming a pharmaceutically acceptable salt or solvate.

Patentansprüche

1. Verbindung der Formel (I):



(I)

worin
A für Phenyl oder einen 5- oder 6-gliedrigen heterocyclischen Ring mit einem oder zwei, unter O, N oder S ausgewählten Heteroatomen steht und gegebenenfalls durch C_{1-6}-Alkyl, Halogen, Nitro, Amino, C_1-C_6-Alkylamino, CF_3, SO_2Me, $NHSO_2Me$ oder Cyano substituiert ist;
B für C=O, NH oder SO_2 steht;
X für C=O, CH(Me), O oder $(CH_2)_p$, worin p 0 oder 1 bedeutet, steht;
Y für O, CH_2, NH oder S steht;
Z für C=O oder SO_2 steht, mit der Maßgabe, daß Y für O, CH_2 oder S steht, wenn Z für C=O steht;
R für Wasserstoff oder C_{1-6}-Alkyl steht;

R^1 für Wasserstoff oder Halogen steht;
R^2 für gegebenenfalls durch CO_2H, CO_2-C_1-C_6-Alkyl, $CONH_2$ substituiertes Phenyl oder OH, NHR^3, $NHCH(R^4)(CHR^5)_nR^6$, NH-R^7-R^8, SO_2NH-C_1-C_6-Alkyl, NHCO-C_1-C_6-Alkyl, $NHSO_2$-C_1-C_6-Alkyl, Morpholin, NR^9R^{10}, phenylsubstituiertes Piperazin, C_1-C_6-Alkoxyphenyl, Pyridyl oder Fluorphenyl steht;
n für 0, 1 oder 2 steht;
R^3 für Wasserstoff, ein bi- oder tricyclisches gesättigtes Ringsystem, das gegebenenfalls ein Stickstoffatom enthält, Piperidinyl, C_1-C_6-Alkylpyrrolidin, Ethinylcyclohexyl, einen 5-gliedrigen aromatischen Ring mit 2 oder 3 Heteroatomen, gegebenenfalls durch C_1-C_6-Alkyl, Cyano oder Hydroxy substituiertes C_{4-6}-Cycloalkyl oder C_{1-8}-Alkyl, das gegebenenfalls in der Alkylkette ein Sauerstoffatom enthält und gegebenenfalls durch einen oder mehrere, unter Ethinyl, Cyano, Fluor, Di-C_1-C_6-alkylamino, Hydroxy, Thio-C_1-C_6-alkyl, CO_2R^{11} oder $CONH_2$ ausgewählte Substituenten substituiert ist, steht;
R^4 für Wasserstoff oder gegebenenfalls durch Hydroxy substituiertes C_1-C_6-Alkyl oder C_1-C_6-Alkoxy steht;
R^5 für Wasserstoff oder Hydroxy steht;
R^6 für CO_2R^{11}, $NHCO_2R^{12}$, $CONH_2$ oder einen 5- oder 6-gliedrigen gesättigten Ring mit einem Sauerstoffatom, einen 5-gliedrigen heterocyclischen Ring mit einem oder zwei, unter O, N oder S ausgewählten Heteroatomen oder gegebenenfalls durch eine oder mehrere, unter C_1-C_6-Alkyl, Hydroxy, Amino, C_1-C_6-Alkoxy oder Nitro ausgewählte Gruppen substituiertes Phenyl steht;
R^6 für C_1-C_6-Alkyl steht;
R^7 für einen Cyclopentanring steht;
R^8 für Phenyl steht;
R^9 und R^{10} unabhängig voneinander für Wasserstoff, Benzyl, Alkenyl, Cycloalkyl, gegebenenfalls durch Hydroxy substituiertes C_1-C_6-Alkyl, C_1-C_6-Alkoxy, Cyano, Di-C_1-C_6-alkylamino, Phenyl, Pyridyl oder CO_2R^{11} stehen oder gemeinsam einen 5- bis 7-gliedrigen gesättigten oder teilweise gesättigten Ring bilden, der gegebenenfalls ein weiteres Heteroatom enthält und gegebenenfalls durch eine oder mehrere, unter C_1-C_6-Alkyl (das gegebenenfalls in der Kette ein Sauerstoffatom enthält und gegebenenfalls durch Hydroxy substituiert ist), CO-C_1-C_6-Alkyl, CO_2R^{11}, $COR^{13}R^{14}$, CHO oder Piperidin ausgewählte Gruppen substituiert ist;
R^{11} für Wasserstoff oder C_1-C_6-Alkyl steht;
R^{12} für C_1-C_6-Alkyl steht; und
R^{13} und R^{14} unabhängig voneinander für Wasserstoff oder C_1-C_6-Alkyl stehen,
oder ein pharmazeutisch unbedenkliches Salz oder Solvat davon.

2. Verbindung nach Anspruch 1, in der A für gegebenenfalls durch C_{1-6}-Alkyl, Halogen, Nitro, Amino, C_1-C_6-Alkylamino, CF_3, SO_2Me, $NHSO_2Me$ oder Cyano substituiertes Phenyl steht.

3. Verbindung nach Anspruch 1 oder 2, in der B für C=O steht.

4. Verbindung nach einem der Ansprüche 1 bis 3, in der X für CH_2, Y für O und Z für C=O steht.

5. Verbindung nach einem der Ansprüche 1 bis 4, in der R für Wasserstoff steht.

6. Verbindung nach einem der Ansprüche 1 bis 5, in der R^1 für Wasserstoff steht.

7. Verbindung nach einem der Ansprüche 1 bis 6, in der R^2 für NR^9R^{10}, worin eine der Gruppen R^9 und R^{10} für Wasserstoff und die andere für C_1-C_6-Alkyl steht, steht.

8. Verbindung nach Anspruch 1, bei der es sich um:

2-({3-Nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]phenyl}carbonyl)benzoesäure,
1-{1-[2-Nitro-4-(phenylcarbonyl)phenyl]piperidin-4-yl}-1,4-dihydro-2H-3,1-benzoxazin-2-on,
2-({3-Nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]phenyl}carbonyl)benzoesäuremethylester,
2-({3-Nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]phenyl}carbonyl)benzamid,
2-({3-Nitro-4-[4-(2-oxo-3,4-dihydrochinolin-1(2H)-yl)piperidin-1-yl]phenyl}carbonyl)benzoesäuremethylester,
2-({3-Nitro-4-[4-(2-oxo-3,4-dihydrochinolin-1(2H)-yl)piperidin-1-yl]phenyl}carbonyl)benzoesäure,
2-({4-[4-(7-Chlor-2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]-3-nitrophenyl}carbonyl)benzoesäuremethylester,
N-(1,1-Dimethylethyl)-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamid,
N-[(1R)-2-Hydroxy-1-(phenylmethyl)ethyl] -3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl] benzamid,

2-[({3-Nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]phenyl}carbonyl)amino]propansäuremethylester,
3-Nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]-N-(tetrahydrofuran-2-ylmethyl)benzamid,
N-[2-(4-Aminophenyl)ethyl]-3-nitro-4-[4- (2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamid,
3-Nitro-4- [4- (2-oxo-2H-3,1-benzoxazin-1(4H)-yl)-piperidin-1-yl]-N-(2,2,2-trifluorethyl)benzamid,
(2S)-3-Methyl-2-[({3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]phenyl}carbonyl)amino]butansäureethylester,
3-Hydroxy-2-[({3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]phenyl}carbonyl)amino]propansäuremethylester,
N-[2-(3,4-Dihydroxyphenyl)ethyl]-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]-benzamid,
3-Nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)-piperidin-1-yl]-N-(2-phenylethyl)benzamid,
N-[(4-Aminophenyl)methyl]-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamid,
3-Nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)-piperidin-1-yl]-N-(2-thien-2-ylethyl)benzamid,
N-[3-(Dimethylamino)-2,2-dimethylpropyl]-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl] benzamid,
N-{[2,4-Bis(methyloxy)phenyl]methyl}-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]-benzamid,
N-Bicyclo[2.2.1]hept-2-yl-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamid,
N-(2-Fluorethyl)-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamid,
3-Nitro-N-[(3-nitrophenyl)methyl]-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamid,
N-[(1S,2R)-2-Hydroxy-1-methyl-2-phenylethyl]-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)-piperidin-1-yl]benzamid,
3-Nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)-piperidin-1-yl]-N-{[3,4,5-tris(methyloxy)phenyl]-methyl}benzamid,
3-Nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)-piperidin-1-yl]-N-(2-phenylcyclopropyl)benzamid,
N-[2-Hydroxy-1-(hydroxymethyl-1-methylethyl]-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)-piperidin-1-yl]benzamid,
N-(1-Azabicyclo[2.2.2]oct-3-yl)-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]-benzamid,
3-Nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)-piperidin-1-yl]-N-(2-piperidin-1-ylethyl)benzamid, N-(1,3-Dimethylbutyl)-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamid,
N-(1-Methylbutyl)-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamid,
N-(1-Methylhexyl)-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamid,
N-(3-Methylbutyl)-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamid,
N-[(2-Aminophenyl)methyl]-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamid,
N-[(2-Hydroxy-1-(hydroxymethyl)ethyl]-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamid,
N-[2-(Ethylthio)ethyl]-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamid,
N-[(1S)-1-(Hydroxymethyl)-2,2-dimethylpropyl]-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)-piperidin-1-yl]benzamid,
N-(4-Methylcyclohexyl)-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamid,
N-{2-Hydroxy-1-[(methyloxy)methyl]-2-phenylethyl}-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)-piperidin-1-yl]benzamid,
N-Ethyl-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamid,
N-Cyclopropyl-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamid,
3-Nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)-piperidin-1-yl]-N-(phenylmethyl)benzamid
N-(1-Methylpropyl)-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamid,
2-[({3-Nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]phenyl}carbonyl)amino]ethylcarbamidsäure-1,1-dimethylethylester,
N-[2-(3,4-Dihydroxyphenyl)ethyl]-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]-benzamid,
N-{[4-(Methyloxy)phenyl]methyl}-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]-benzamid,
N-[2-(1H-Imidazol-4-yl)ethyl]-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]-benzamid,
N-[(1S)-1-(Hydroxymethyl)propyl]-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]-benzamid,
3-Nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)-piperidin-1-yl]-N-[1-(phenylmethyl)piperidin-4-yl]benzamid
N-[(1R)-1-(Hydroxymethyl)propyl]-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]-benzamid,
N-(4-Hydroxybutyl)-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamid,
3-Nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)-piperidin-1-yl]-N-tricyclo[3.3.1.1~3,7~]dec-1-ylbenzamid,
N-[(1S,2S)-2-Hydroxycyclohexyl]-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]-benzamid,
N-(2-Hydroxy-1-methylethyl)-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]-benzamid,

N-{2-[(2-Hydroxyethyl)oxy]ethyl}-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]-benzamid,
N-[1-(Hydroxymethyl)butyl]-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamid,
N-(2-Amino-2-oxoethyl)-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamid,
N-[1-(4-Fluorphenyl)ethyl]-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamid,
3-Nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)-piperidin-1-yl]-N-(3-phenylpropyl)benzamid,
N-[(1S,2R)-2-Hydroxycyclohexyl]-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]-benzamid,
3-Hydroxy-2-[({3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]phenyl}carbonyl)amino]propansäureethylester,
N-[(1R,2S)-2-Hydroxy-1-methyl-2-phenylethyl]-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)-piperidin-1-yl]benzamid,
1-{1-[4-(Morpholin-4-ylcarbonyl)-2-nitrophenyl]-piperidin-4-yl}-1,4-dihydro-2H-3,1-benzoxazin-2-on,
N,N-Dimethyl-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamid,
N,N-Bis(2-hydroxyethyl)-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamid,
N-(2-Hydroxyethyl)-N-methyl-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]-benzamid,
N-(2-Hydroxyethyl)-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]-N-(phenylmethyl)benzamid,
1-(1-{2-Nitro-4-[(4-phenylpiperazin-1-yl)-carbonyl]phenyl}piperidin-4-yl)-1,4-dihydro-2H-3,1-benzoxazin-2-on,
N-[(1S,2R)-2-Hydroxy-1-methyl-2-phenylethyl]-N-methyl-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl) piperidin-1-yl]benzamid,
N-Ethyl-N-(2-hydroxyethyl)-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamid,
1-[1-(4-{[4-(4-Fluorphenyl)piperazin-1-yl]-carbonyl}-2-nitrophenyl)piperidin-4-yl]-1,4-dihydro-2H-3,1-benzoxazin-2-on,
1-{1-[4-(Azepan-1-ylcarbonyl)-2-nitrophenyl]-piperidin-4-yl}-1,4-dihydro-2H-3,1-benzoxazin-2-on,
N,N-Diethyl-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamid,
N-[2-(Dimethylamino)ethyl]-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]-N-(phenylmethyl) benzamid,
N-Ethyl-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]-N-(phenylmethyl)benzamid,
N-Butyl-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]-N-(phenylmethyl)benzamid,
1-{1-[2-Nitro-4-(piperidin-1-ylcarbonyl)phenyl]-piperidin-4-yl}-1,4-dihydro-2H-3,1-benzoxazin-2-on,
[({3-Nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]phenyl}carbonyl)(phenylmethyl)-amino]essigsäureethylester,
N-(2-Hydroxyethyl)-N-(1-methylethyl)-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]-benzamid,
1-(1-{2-Nitro-4-[(4-pyridin-2-ylpiperazin-1-yl)-carbonyl]phenyl}piperidin-4-yl)-1,4-dihydro-2H-3,1-benzoxazin-2-on,
1-{1-[2-Nitro-4-(pyrrolidin-1-ylcarbonyl)phenyl]-piperidin-4-yl}-1,4-dihydro-2H-3,1-benzoxazin-2-on,
N-(2-Hydroxyethyl)-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]-N-pentylbenzamid,
N-[2-(Diethylamino)ethyl]-N-ethyl-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]-benzamid,
N-Ethyl-N-methyl-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamid,
(2S)-1-({3-Nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]phenyl}carbonyl)-pyrrolidin-2-carbonsäureamid,
N-(2-Cyanoethyl)-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]-N-(phenylmethyl)benzamid,
1-(1-{4-[(3,5-Dimethylpiperidin-1-yl)carbonyl]-2-nitrophenyl}piperidin-4-yl)-1,4-dihydro-2H-3,1-benzoxazin-2-on,
1-[1-(4-{[(2R,6S)-2,6-Dimethylmorpholin-4-yl]-carbonyl}-2-nitrophenyl)piperidin-4-yl]-1,4-dihydro-2H-3,1-benzoxazin-2-on,
1-{1-[4-({4-[2-(Methyloxy)phenyl]piperazin-1-yl}carbonyl)-2-nitrophenyl]piperidin-4-yl}-1,4-dihydro-2H-3,1-benzoxazin-2-on,
1-{1-[2-Nitro-4-(thiomorpholin-4-ylcarbonyl)-phenyl]piperidin-4-yl}-1,4-dihydro-2H-3,1-benzoxazin-2-on,
1-(1-{4-[(4-{2-[(2-Hydroxyethyl)oxy]ethyl}piperazin-1-yl)carbonyl]-2-nitrophenyl}piperidin-4-yl)-1,4-dihydro-2H-3,1-benzoxazin-2-on,
N-Ethyl-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]-N-(pyridin-4-ylmethyl)-benzamid,
N-Methyl-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]-N-prop-2-inylbenzamid,
1-(1-{4-[(4-Acetylpiperazin-1-yl)carbonyl]-2-nitrophenyl}piperidin-4-yl)-1,4-dihydro-2H-3,1-benzoxazin-2-on,
1-[1-(4-{[2-(Hydroxymethyl)piperidin-1-yl]-carbonyl}-2-nitrophenyl)piperidin-4-yl]-1,4-dihydro-2H-3,1-benzoxazin-2-on,
4-({3-Nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]phenyl}carbonyl)piperazin-1-carbaldehyd,

N-Methyl-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]-N-(phenylmethyl)benzamid,
4-({3-Nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]phenyl}carbonyl)piperazin-1-carbonsäureethylester,
1-({3-Nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]phenyl}carbonyl)piperazin-4-carbonsäureethylester,
1-({3-Nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]phenyl}carbonyl)piperidin-3-carbonsäureamid,
1-(1-{4-[(4-Methylpiperazin-1-yl)carbonyl]-2-nitrophenyl}piperidin-4-yl)-1,4-dihydro-2H-3,1-benzoxazin-2-on,
1-{1-[4-(2,5-Dihydro-1H-pyrrol-1-ylcarbonyl)-2-nitrophenyl]piperidin-4-yl}-1,4-dihydro-2H-3,1-benzoxazin-2-on,
N-Ethyl-N-(2-methylprop-2-enyl)-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]-benzamid,
N,N-Bis(cyanomethyl)-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamid,
N-Butyl-N-(cyanomethyl)-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamid,
N,N-Bis(2-hydroxypropyl)-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamid,
1-(1-{4-[(4-Hydroxypiperidin-1-yl)carbonyl]-2-nitrophenyl}piperidin-4-yl)-1,4-dihydro-2H-3,1-benzoxazin-2-on,
1-(1-{4-[(2,5-Dimethyl-2,5-dihydro-1H-pyrrol-1-yl)carbonyl]-2-nitrophenyl}piperidin-4-yl)-1,4-dihydro-2H-3,1-benzoxazin-2-on,
N-Methyl-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]-N-propylbenzamid,
N-(2-Amino-2-oxoethyl)-N-methyl-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]-benzamid,
N,N-Diethyl-1-({3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]phenyl}carbonyl)piperidin-3-carbonsäureamid,
N-Cyclohexyl-N-methyl-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamid,
N-[2-(Methyloxy)ethyl]-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamid,
N-(1-Methylethyl)-6-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]pyridin-3-carbonsäureamid,
5-Chlor-N-(1-methylethyl)-6-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]pyridin-3-carbonsäureamid,
N-(1-Methylethyl)-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzolsulfonamid,
1-[1-(4-Amino-2-chlorphenyl)piperidin-4-yl]-1,4-dihydro-2H-3,1-benzoxazin-2-on,
3-Cyano-N-(1-methylethyl)-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamid,
N-{3-Chlor-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]phenyl}-2-methylpropanamid,
N-{3-Chlor-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]phenyl}propan-2-sulfonamid,
N-{3-Chlor-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]phenyl}-1-cyanocyclopropancarbonsäureamid,
(2S)-N-{3-Chlor-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]phenyl}-1-methylpyrrolidin-2-carbonsäureamid,
5-Chlor-N-(1-methylethyl)-6-[4-(4-methyl-2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]pyridin-3-carbonsäureamid,
(±)-5-Chlor-N-(1-methylethyl)-6-[(cis)-3-methyl-4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]-pyridin-3-carbonsäureamid,
(±)-5-Chlor-N-(1-methylethyl)-6-[(trans)-3-methyl-4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]pyridin-3-carbonsäureamid,
2-[4-(2-Oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]-N-(1,3,4-thiadiazol-2-yl)-4-(trifluormethyl)pyrimidin-5-carbonsäureamid,
2-[4-(2-Oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]-N-(1H-1,2,4-triazol-3-yl)-4-(trifluormethyl)pyrimidin-5-carbonsäureamid,
2-[4-(2-Oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]-N-(1H-pyrazol-3-yl)-4-(trifluormethyl)-pyrimidin-5-carbonsäureamid,
N-(4-Hydroxycyclohexyl)-2-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]-4-(trifluormethyl)pyrimidin-5-carbonsäureamid,
N-[1-(Hydroxymethyl)propyl]-2-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]-4-(trifluormethyl)pyrimidin-5-carbonsäureamid,
N-(3-Hydroxy-2,2-dimethylpropyl)-2-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]-4-(trifluormethyl)pyrimidin-5-carbonsäureamid,
2-[4-(2-Oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin1-yl]-N-(tetrahydrofuran-2-ylmethyl)-4-(trifluormethyl)pyrimidin-5-carbonsäureamid,
N-Cyclobutyl-2-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]-4-(trifluormethyl)pyrimidin-5-carbonsäureamid,

N-Cyclopentyl-2-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]-4-(trifluormethyl)pyrimidin-5-carbonsäureamid,
N-[2-(1H-Imidazol-4-yl)ethyl]-2-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]-4-(trifluormethyl)pyrimidin-5-carbonsäureamid,
N-(1-Ethinylcyclohexyl)-2-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]-4-(trifluormethyl)pyrimidin-5-carbonsäureamid,
N-[(1R)-1-(Hydroxymethyl)-2-methylpropyl]-2-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]-4-(trifluormethyl)pyrimidin-5-carbonsäureamid,
N-(2-Hydroxy-1,1-dimethylethyl)-2-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]-4-(trifluormethyl)pyrimidin-5-carbonsäureamid,
N-(1,1-Diethylprop-2-inyl)-2-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]-4-(trifluormethyl)pyrimidin-5-carbonsäureamid,
N-(2-Hydroxy-1-methylethyl)-2-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]-4-(trifluormethyl)pyrimidin-5-carbonsäureamid,
N-[1-Methyl-2-(methyloxy)ethyl]-2-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl)-4-(trifluormethyl)pyrimidin-5-carbonsäureamid,
N-(1-Methylethyl)-2-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]pyrimidin-5-carbonsäureamid,
N-(1-Methylethyl)-2-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]-1,3-thiazol-4-carbonsäureamid,
N-(1-Methylethyl)-3-methylsulfonyl-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamid,
N-[(1R)-1-(Aminocarbonyl)-2-methylpropyl]-5-chlor-6-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin1-yl]pyridin-3-carbonsäureamid,
5-Chlor-N-[2-hydroxy-1-methylethyl)-6-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]pyridin-3-carbonsäureamid,
5-Chlor-N-(1,1-dimethylprop-2-inyl)-6-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]pyridin-3-carbonsäureamid,
N-(2-Amino-1-cyano-2-oxoethyl)-5-chlor-6-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]-pyridin-3-carbonsäureamid,
N-[(1R)-1-(Aminocarbonyl)-3-methylbutyl]-5-chlor-6-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]pyridin-3-carbonsäureamid,
N-[(1S)-1-(Aminocarbonyl)-2-methylpropyl]-5-chlor-6-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]pyridin-3-carbonsäureamid,
N-[(1S)-1-(Aminocarbonyl)-3-methylbutyl]-5-chlor-6-[4-(2-oxo-2H-3,l-benzoxazin-1(4H)-yl)piperidin1-yl]pyridin-3-carbonsäureamid,
5-Chlor-N-(1-methylethyl)-6-[4-(3-oxo-2,3-dihydro-4H-1,4-benzoxazin-4-yl)piperidin-1-yl]pyridin-3-carbonsäureamid,
N-(l-Methylethyl)-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamid,
N-[(1S)-1-(Aminocarbonyl)-2-methylbutyl]-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamid,
N-(1-Methylethyl)-2-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]-4-(trifluormethyl)-5-pyrimidin-5-carbonsäureamid,
3-Chlor-N-(1-methylethyl)-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamid,
3-Amino-N-(1-methylethyl)-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamid,
N-(1-Methylethyl)-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamid,
N-[(1S)-1-(Aminocarbonyl)-3-methylbutyl]-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamid,
3-(Ethylamino)-N-(1-methylethyl)-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamid,
3-(Diethylamino)-N-(1-methylethyl)-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]benzamid,
N-(1-Methylethyl)-3-[(methylsulfonyl)amino]-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)piperidin-1-yl]-benzamid,
5-Chlor-N-(1-methylethyl)-6-[4-(2-oxo-1,3-benzoxazol-3(2H)-yl)piperidin-1-yl]pyridin-3-carbonsäureamid,
N-(1-Methylethyl)-3-nitro-4-[4-(2-oxo-3,4-dihydrochinolin-1(2H)-yl)piperidin-1-yl]benzamid,
4-[4-(7-Chlor-2-oxo-2H-3,1-benzoxazin-1(4H)-yl)-piperidin-1-yl]-N-(1-methylethyl)-3-nitrobenzamid,
5-Chlor-N-(1-methylethyl)-6-[4-(2-oxo-3,4-dihydrochinolin-1(2H)-yl)piperidin-l-yl]pyridin-3-carbonsäureamid,
4-[4-(2,2-Dioxido-3,4-dihydro-1H-1,2,3-benzothiadiazin-1-yl)piperidin-1-yl]-N-(1-methylethyl)-3-nitrobenzamid

oder ein pharmazeutisch unbedenkliches Salz oder Solvat davon handelt.

9. Pharmazeutische Zusammensetzung, enthaltend eine Verbindung nach einem der Ansprüche 1 bis 8 zusammen

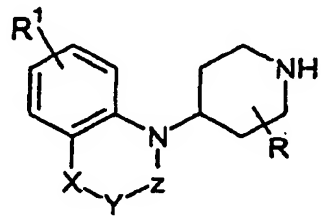
mit einem pharmazeutisch unbedenklichen Hilfsstoff, Verdünnungsmittel oder Träger.

10. Verbindung nach einem der Ansprüche 1 bis 8 zur Verwendung bei der Therapie.

11. Verbindung nach einem der Ansprüche 1 bis 8 zur Verwendung bei der Behandlung von rheumatoider Arthritis.

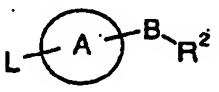
12. Verwendung einer Verbindung nach einem der Ansprüche 1 bis 8 bei der Herstellung eines Arzneimittels zur Verwendung bei der Therapie.

13. Verfahren zur Herstellung einer Verbindung der Formel (I) gemäß Anspruch 1, bei dem man eine Verbindung der Formel (II)



(II)

worin R, R^1, X, Y und Z die bei Formel (I) angegebene Bedeutung besitzen oder für ein geschütztes Derivat davon stehen, mit einer Verbindung der Formel (III)



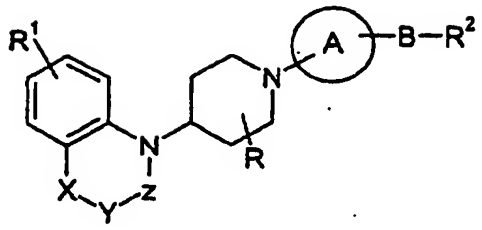
(III)

worin B und R^2 die bei Formel (I) angegebene Bedeutung besitzen oder für ein geschütztes Derivat davon stehen und L für eine Abgangsgruppe steht, umsetzt und danach gegebenenfalls in beliebiger Reihenfolge:

- eine oder mehrere funktionelle Gruppen in weitere funktionelle Gruppen umwandelt
- jegliche Schutzgruppen abspaltet
- ein pharmazeutisch unbedenkliches Salz oder Solvat herstellt.

Revendications

1. Composé de formule (I) :



(I)

dans laquelle
A est phényle ou un noyau hétérocyclique à 5 ou 6 chaînons contenant un ou deux hétéroatomes choisis parmi O, N ou S ; et substitué éventuellement par alkyle en C_{1-6}, halogène, nitro, amino, alkylamino en C_{1-6}, CF_3, SO_2Me, $NHSO_2Me$ ou cyano ;
B est C=O, NH ou SO_2 ;
X est C=O, CH(Me), O ou $(CH_2)p$ où p est 0 ou 1 ;
Y est O, CH_2, NH ou S ;
Z est C=O ou SO_2, à condition que lorsque Z est C=O alors Y est O, CH_2 ou S ;
R est hydrogène ou alkyle en C_{1-6} ;
R^1 est hydrogène, halogène ;
R^2 est phényle éventuellement substitué par CO_2H, alkyle en CO_2-C_1-C_6, $CONH_2$ ou R^2 est OH, NHR^3, NHCH (R^4) $(CHR^5)_nR^6$,NH-R^7-R^8, SO_2NHC_1-C_6alkyle, $NHCOC_1$-C_6alkyle, $NHSO_2C_1$-C_6alkyle, morpholine, NR^9R^{10}, pipérazine substituée par phényle, alcoxyphényle en C_1-C_6, pyridyle ou fluorophényle ;
n est 0, 1 ou 2 ;
R^3 est hydrogène, un système de noyaux bi- ou tricyclique saturés contenant éventuellement un atome d'azote, pipéridinyle, alkylpyrrolidine en C_1-C_6, éthynylcyclohexyle, un noyau aromatique à 5 chaînons contenant 2 ou 3 hétéroatomes, cycloaklyle en C_{4-6} éventuellement substitué par alkyle en C_1-C_6, cyano ou hydroxy, ou alkyle en C_{1-8} contenant éventuellement un atome d'oxygène dans la chaîne alkyle et étant éventuellement substitué par un ou plusieurs substituants choisis parmi éthynyle, cyano, fluoro, dialkylamino en C_1-C_6, hydroxy, thioalkyle en C_1-C_6, CO_2R^{11} ou $CONH_2$;
R^4 est hydrogène ou alkyle en C_1-C_6 éventuellement substitué par hydroxy ou alcoxy en C_1-C_6 ;
R^5 est hydrogène ou hydroxy ;
R^6 est CO_2R^{11}, $NHCO_2R^{12}$, $CONH_2$ ou un noyau saturé à 5 ou 6 chaînons contenant un atome d'oxygène, un noyau hétérocyclique à 5 chaînons contenant un ou deux hétéroatomes choisis parmi O, N ou S, ou phényle éventuellement substitué par un ou deux groupements choisis parmi alkyle en C_1-C_6, hydroxy, amino, alcoxy en C_1-C_6, ou nitro ;
R^6 est alkyle en C_1-C_6 ;
R^7 est un noyau cyclopentane ;
R^8 est phényle ;
R^9 et R^{10} sont indépendamment hydrogène, benzyle, alcényle, cycloalkyle, alkyle en C_1-C_6 éventuellement substitué par hydroxy, alcoxy en C_1-C_6, cyano, dialkylamino en C_1-C_6, phényle, pyridyle ou CO_2R^{11} ou R^9 et R^{10} forment ensemble un noyau saturé ou partiellement saturé à 5 à 7 chaînons contenant éventuellement un autre hétéroatome et substitué éventuellement par un ou plusieurs groupements choisis parmi alkyle en C_1-C_6 (contenant éventuellement un atome d'oxygène dans la chaîne et substitué éventuellement par hydroxy), CO-alkyle en C_1-C_6, CO_2R^{11}, $COR^{13}R^{14}$, CHO ou pipéridine ;
R^{11} est hydrogène ou alkyle en C_1-C_6 ;
R^{12} est alkyle en C_1-C_6 ; et
R^{13} et R^{14} sont indépendamment hydrogène ou alkyle en C_1-C_6,
ou un sel ou solvate pharmaceutiquement acceptable de celui-ci.

2. Composé selon la revendication 1, **caractérisé en ce que** A est phényle éventuellement substitué par alkyle en C_{1-6}, halogène, nitro, amino, alkylamino en C_1-C_6, CF_3, SO_2Me, $NHSO_2Me$ ou cyano.

3. Composé selon la revendication 1 ou 2, **caractérisé en ce que** B est C=O.

4. Composé selon l'une quelconque des revendications 1 à 3, **caractérisé en ce que** X est CH_2, Y est O et Z est C=O.

5. Composé selon l'une quelconque des revendications 1 à 4, **caractérisé en ce que** R est hydrogène.

6. Composé selon l'une quelconque des revendications 1 à 5, **caractérisé en ce que** R^1 est hydrogène.

7. Composé selon l'une quelconque des revendications 1 à 6, **caractérisé en ce que** R^2 est NR^9R^{10} où l'un de R^9 ou R^{10} est hydrogène et l'autre est alkyle en C_1-C_6.

8. Composé selon la revendication 1, **caractérisé en ce qu'**il s'agit des composés suivants :

l'acide 2-({3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)pipéridin-1-yl]phényl}carbonyl)benzoïque,
la 1-{1-[2-nitro-4-(phénylcarbonyl)phényl]pipéridin-4-yl}-1,4-dihydro-2H-3,1-benzoxazin-2-one,
le 2-({3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)pipéridin-1-yl]phényl}carbonyl)benzoate de méthyle,
le 2-({3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)pipéridin-1-yl]phényl}carbonyl)benzamide,
le 2-({3-nitro-4-[4-(2-oxo-3,4-dihydroquinoléin-1(2H)-yl)pipéridin-1-yl)phényl}carbonyl)benzoate de méthyle,
l'acide 2-({3-nitro-4-[4-(2-oxo-3,4-dihydroquinoléin-1(2H)-yl)pipéridin-1-yl]phényl}carbonyl)benzoïque,
le 2-({4-[4-(7-chloro-2-oxo-2H-3,1-benzoxazin-1(4H)-yl)pipéridin-1-yl]-3-nitrophényl}carbonyl)benzoate de méthyle,
le N-(1,1-diméthyléthyl)-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)pipéridin-1-yl]benzamide,
le N-[(1R)-2-hydroxy-1-(phénylméthyl)éthyl]-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)pipéridin-1-yl]benzamide,
le 2-[({3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)pipéridin-1-yl]phényl}carbonyl)amino]propanoate de méthyle,
le 3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)pipéridin-1-yl]-N-(tétrahydrofuran-2-ylméthyl)benzamide,
le N-[2-(4-aminophényl)éthyl]-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)pipéridin-1-yl]benzamide,
le 3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)pipéridin-1-yl]-N-(2,2,2-trifluoroéthyl)benzamide,
le (2S)-3-méthyl-2-[({3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)pipéridin-1-yl]phényl}carbonyl)amino]butanoate d'éthyle,
le 3-hydroxy-2-[({3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)pipéridin-1-yl]phényl}carbonyl)amino]propanoate de méthyle,
le N-[2-(3,4-dihydroxyphényl)éthyl]-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)pipéridin-1-yl]benzamide,
le 3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)pipéridin-1-yl]-N-(2-phényléthyl)benzamide,
le N-[(4-aminophényl)méthyl]-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)pipéridin-1-yl]benzamide,
le 3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)pipéridin-1-yl]-N-(2-thién-2-yléthyl)benzamide,
le N-[3-(diméthylamino)-2,2-diméthylpropyl]-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)pipéridin-1-yl]benzamide,
le N-{[2,4-bis(méthyloxy)phényl]méthyl}-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)pipéridin-1-yl]benzamide,
le N-bicyclo[2,2,1]hept-2-yl-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)pipéridin-1-yl]benzamide,
le N-(2-fluoroéthyl)-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)pipéridin-1-yl]benzamide,
le 3-nitro-N-[(3-nitrophényl)méthyl]-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)pipéridin-1-yl]benzamide,
le N-[(1S,2R)-2-hydroxy-1-méthyl-2-phényléthyl]-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)pipéridin-1-yl]benzamide,
le 3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)-pipéridin-1-yl]-N-{[3,4,5-tris(méthyloxy)phényl]méthyl}-benzamide,
le 3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)pipéridin-1-yl]-N-(2-phénylcyclopropyl)benzamide,
le N-[2-hydroxy-1-(hydroxyméthyl)-1-méthyléthyl]-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)pipéridin-1-yl]benzamide,
le N-(1-azabicyclo[2,2,2]oct-3-yl)-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)pipéridin-1-yl]benzamide,
le 3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)pipéridin-1-yl]-N-(2-pipéridin-1-yléthyl)benzamide,
le N-(1,3-diméthylbutyl)-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)pipéridin-1-yl]benzamide,
le N-(1-méthylbutyl)-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)pipéridin-1-yl]benzamide,
le N-(1-méthylhexyl)-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)pipéridin-1-yl]benzamide,
le N-(3-méthylbutyl)-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)pipéridin-1-yl]benzamide,
le N-[(2-aminophényl)méthyl]-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)pipéridin-1-yl]benzamide,
le N-[2-hydroxy-1-(hydroxyméthyl)éthyl]-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)pipéridin-1-yl]ben-

zamide,
le N-[2-(éthylthio)éthyl]-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)pipéridin-1-yl]benzamide,
le N-[(1S)-1-(hydroxyméthyl)-2,2-diméthylpropyl]-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)pipéridin-1-yl]benzamide,
le N-(4-méthylcyclohexyl)-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)pipéridin-1-yl]benzamide,
le N-{2-hydroxy-1-[(méthyloxy)méthyl]-2-phényléthyl}-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)pipéridin-1-yl]benzamide,
le N-éthyl-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)pipéridin-1-yl]benzamide,
le N-cyclopropyl-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)pipéridin-1-yl]benzamide,
le 3-nitro-4-[4-(2-oxo-2H-3,l-benzoxazin-1(4H)-yl)pipéridin-1-yl]N-(phénylméthyl)benzamide,
le N-(1-méthylpropyl)-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)pipéridin-1-yl]benzamide,
le 2-[({3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)pipéridin-1-yl]phényl}carbonyl)amino]éthylcarbamate de 1,1-diméthyléthyle,
le N-[2-(3,4-dihydroxyphényl)éthyl]-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)pipéridin-1-yl]benzamide,
le N-{[4-(méthyloxy)phényl]méthyl}-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)pipéridin-1-yl]benzamide,
le N-[2-(1H-imidazol-4-yl)éthyl]-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)pipéridin-1-yl]benzamide,
le N-[(1S)-1-(hydroxyméthyl)propyl]-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)pipéridin-1-yl]benzamide,
le 3-nitro-4-[4-(2-oxo-2H-3,l-benzoxazin-1(4H)-yl)pipéridin-1-yl]-N-[1-(phénylméthyl)pipéridin-4-yl]benzamide,
le N-[(1R)-1-(hydroxyméthyl)propyl]-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)pipéridin-1-yl]benzamide,
le N-(4-hydroxybutyl)-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)pipéridin-1-yl]benzamide,
le 3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-l(4H)-yl)pipéridin-1-yl]-N-tricyclo[3,3,1,1~3,7~]-déc-1-ylbenzamide,
le N-[(1S,2S)-2-hydroxycyclohexyl)-3-vitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)pipéridin-1-yl]benzamide,
le N-(2-hydroxy-1-méthyléthyl)-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)pipéridin-1-yl]benzamide,
le N-{2-[(2-hydroxyéthyl)oxy]éthyl}-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)pipéridin-1-yl]benzamide,
le N-[1-(hydroxyméthyl)butyl]-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)pipéridin-1-yl]benzamide,
le N-(2-amino-2-oxoéthyl)-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)pipéridin-1-yl]benzamide,
le N-[1-(4-fluorophényl)éthyl]-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)pipéridin-1-yl]benzamide,
le 3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)pipéridin-1-yl]-N-(3-phénylpropyl)benzamide,
le N-[(1S,2R)-2-hydroxycyclohexyl]-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)pipéridin-1-yl]benzamide,
le 3-hydroxy-2-[({3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)pipéridin-1-yl]phényl}carbonyl)amino] propanoate d'éthyle,
le N-[(1R,2S)-2-hydroxy-1-méthyl-2-phényléthyl]-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)pipéridin-1-yl]benzamide,
la 1-{1-[4-(morpholin-4-ylcarbonyl)-2-nitrophényl]pipéridin-4-yl}-1,4-dihydro-2H-3,1-benzoxazin-2-one,
le N,N-diméthyl-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)pipéridin-1-yl]benzamide,
le N,N-bis(2-hydroxyéthyl)-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)pipéridin-1-yl]benzamide,
le N-(2-hydroxyéthyl)-N-méthyl-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)pipéridin-1-yl]benzamide,
le N-(2-hydroxyéthyl)-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)pipéridin-1-yl]-N-(phénylméthyl)benzamide,
la 1-(1-{2-nitro-4-[(4-phénylpipérazin-1-yl)carbonyl]phényl}pipéridin-4-yl)-1,4-dihydro-2H-3,1-benzoxazin-2-one,
le N-[(1S,2R)-2-hydroxy-1-méthyl-2-phényléthyl]-N-méthyl-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl) pipéridin-1-yl]benzamide,
le N-éthyl-N-(2-hydroxyéthyl)-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)pipéridin-1-yl]benzamide,
la 1-[1-(4-{[4-(4-fluorophényl)pipérazin-1-yl]carbonyl}-2-nitrophényl)pipéridin-4-yl]-1,4-dihydro-2H-3,1-benzoxazin-2-one,
la 1-{1-[4-(azépan-1-ylcarbonyl)-2-nitrophényl]-pipéridin-4-yl}-1,4-dihydro-2H-3,1-benzoxazin-2-one,
le N,N-diéthyl-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)pipéridin-1-yl]benzamide,
le N-[2-(diméthylamino)éthyl]-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)pipéridin-1-yl]-N-(phénylméthyl)benzamide,

le N-éthyl-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)pipéridin-1-yl]-N-(phénylméthyl)benzamide,
le N-butyl-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)pipéridin-1-yl]-N-(phénylméthyl)benzamide,
la 1-{1-[2-nitro-4-(pipéridin-1-ylcarbonyl)phényl]-pipéridin-4-yl}-1,4-dihydro-2H-3,1-benzoxazin-2-one,
le [({3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)pipéridin-1-yl]phényl}carbonyl)(phénylméthyl)amino]-acétate d'éthyle,
le N-(2-hydroxyéthyl)-N-(1-méthyléthyl)-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)pipéridin-1-yl]benzamide,
la 1-(1-{2-nitro-4-[(4-pyridin-2-ylpipérazin-1-yl)carbonyl]phényl}pipéridin-4-yl)-1,4-dihydro-2H-3,1-benzoxazin-2-one,
la 1-{1-[2-nitro-4-(pyrrolidin-1-ylcarbonyl)phényl]-pipéridin-4-yl}-1,4-dihydro-2H-3,1-benzoxazin-2-one,
le N-(2-hydroxyéthyl)-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)pipéridin-1-yl]-N-pentylbenzamide,
le N-[2-(diéthylamino)éthyl]-N-éthyl-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)pipéridin-1-yl]benzamide,
le N-éthyl-N-méthyl-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)pipéridin-1-yl]benzamide,
le (2S)-1-({3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)pipéridin-1-yl]phényl}carbonyl)pyrrolidine-2-carboxamide,
le N-(2-cyanoéthyl)-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)pipéridin-1-yl]-N-(phénylméthyl)benzamide,
la 1-(1-{4-[(3,5-diméthylpipéridin-1-yl)carbonyl]-2-nitrophényl}pipéridin-4-yl)-1,4-dihydro-2H-3,1-benzoxazin-2-one,
la 1-[1-(4-{[(2R,6S)-2,6-diméthylmorpholin-4-yl]carbonyl}-2-nitrophényl)pipéridin-4-yl]-1,4-dihydro-2H-3,1-benzoxazin-2-one,
la 1-{1-[4-({4-[2-(méthyloxy)phényl]pipérazin-1-yl}carbonyl)-2-nitrophényl]pipéridin-4-yl}-1,4-dihydro-2H-3,1-benzoxazin-2-one,
la 1-{1-[2-nitro-4-(thiomorpholin-4-yl-carbonyl)phényl]pipéridin-4-yl}-1,4-dihydro-2H-3,1-benzoxazin-2-one,
la 1-(1-{4-[(4-{2-[(2-hydroxyéthyl)oxy]éthyl}pipérazin-1-yl)carbonyl]-2-nitrophényl}pipéridin-4-yl)-1,4-dihydro-2H-3,1-benzoxazin-2-one,
le N-éthyl-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)pipéridin-1-yl]-N-(pyridin-4-ylméthyl)benzamide,
le N-méthyl-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)pipéridin-1-yl]-N-prop-2-ynylbenzamide,
la 1-(1-{4-[(4-acétylpipérazin-1-yl)carbonyl]-2-nitrophényl}pipéridin-4-yl)-1,4-dihydro-2H-3,1-benzoxazin-2-one,
la 1-[1-(4-{[2-(hydroxyméthyl)pipéridin-1-yl]carbonyl}-2-nitrophényl)pipéridin-4-yl]-1,4-dihydro-2H-3,1-benzoxazin-2-one,
le 4-({3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)pipéridin-1-yl]phényl}carbonyl)pipérazine-1-carbaldéhyde,
le N-méthyl-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)pipéridin-1-yl]-N-(phénylméthyl)benzamide,
le 4-({3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)pipéridin-1-yl]phényl}carbonyl)pipérazine-1-carboxylate d'éthyle,
le 1-({3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)pipéridin-1-yl]phényl}carbonyl)pipéridine-2-carboxylate d'éthyle,
le 1-({3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)pipéridin-1-yl]phényl}-carbonyl)pipéridine-3-carboxamide,
la 1-(1-{4-[(4-méthylpipérazin-1-yl)carbonyl]-2-nitrophényl}pipéridin-4-yl)-1,4-dihydro-2H-3,1-benzoxazin-2-one,
la 1-{1-[4-(2,5-dihydro-1H-pyrrol-1ylcarbonyl)-2-nitrophényl]pipéridin-4-yl}-1,4-dihydro-2H-3,1-benzoxazin-2-one,
le N-éthyl-N-(2-méthylprop-2-ényl)-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)pipéridin-1-yl]benzamide,
le N,N-bis(cyanométhyl)-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)pipéridin-1-yl]benzamide,
le N-butyl-N-(cyanométhyl)-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)pipéridin-1-yl]benzamide,
le N,N-bis(2-hydroxypropyl)-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)pipéridin-1-yl]benzamide,
la 1-(1-{4-[(4-hydroxypipéridin-1-yl)carbonyl]-2-nitrophényl}pipéridin-4-yl)-1,4-dihydro-2H-3,1-benzoxazin-2-one,
la 1-(1-{4-[(2,5-diméthyl-2,5-dihydro-1H-pyrrol-1-yl)carbonyl]-2-nitrophényl}pipéridin-4-yl)-1,4-dihydro-2H-3,1-benzoxazin-2-one,
le N-méthyl-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)pipéridin-1-yl]-N-propylbenzamide,
le N-(2-amino-2-oxoéthyl)-N-méthyl-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)pipéridin-1-yl]benzamide,
le N,N-diéthyl-1-({3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)pipéridin-1-yl]phényl}carbonyl)pipéridine-

3-carbomaxide,
le N-cyclohexyl-N-méthyl-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)pipéridin-1-yl]benzamide,
le N-[2-(méthyloxy)éthyl]-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)pipéridin-l-yl]benzamide,
le N-(1-méthyléthyl)-6-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)pipéridin-1-yl]pyridine-3-carboxamide,
le 5-chloro-N-(1-méthyléthyl)-6-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)pipéridin-1-yl]pyridine-3-carboxamide,
le N-(1-méthyléthyl)-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)pipéridin-1-yl]benzènesulfonamide,
la 1-[1-(4-amino-2-chlorophényl)pipéridin-4-yl]-1,4-dihydro-2H-3,1-benzoxazin-2-one,
le 3-cyano-N-(1-méthyléthyl)-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)pipéridin-1-yl]benzamide,
le N-{3-chloro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)pipéridin-1-yl]phényl}-2-méthylpropanamide,
le N-{3-chloro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)pipéridin-1-yl]phényl}propane-2-sulfonamide,
le N-{3-chloro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)pipéridin-1-yl]phényl}-1-cyanocyclopropanecarboxamide,
le (2S)-N-{3-chloro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)pipéridin-1-yl]phényl}-1-méthylpyrrolidine-2-carboxamide,
le 5-chloro-N-(1-méthyléthyl)-6-[4-(4-méthyl-2-oxo-2H-3,1-benzoxazin-1(4H)-yl)pipéridin-1-yl]pyridine-3-carboxamide,
le ±-5-chloro-N-(1-méthyléthyl)-6-[(cis)-3-méthyl-4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)pipéridin-1-yl]pyridine-3-carboxamide,
le ±-5-chloro-N-(1-méthyléthyl)-6-[(trans)-3-méthyl-4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)pipéridin-1-yl]pyridine-3-carboxamide,
le 2-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)pipéridin-1-yl]-N-(1,3,4-thiadiazol-2-yl)-4-(trifluorométhyl)pyrimidine-5-carboxamide,
le2-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)pipéridin-1-yl]-N-(1H-1,2,4-triazol-3-yl)-4-(trifluorométhyl)pyrimidine-5-carboxamide,
le 2-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)pipéridin-1-yl]-N-(1H-pyrazol-3-yl)-4-(trifluorométhyl)pyrimidine-5-carboxamide,
le N-(4-hydroxycyclohexyl)-2-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)pipéridin-1-yl]-4-(trifluorométhyl)pyrimidine-5-carboxamide,
le N-[1-(hydroxyméthyl)propyl)-2-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)pipéridin-1-yl]-4-(trifluorométhyl)pyrimidine-5-carboxamide,
le N-(3-hydroxy-2,2-diméthylpropyl)-2-(4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)pipéridin-1-yl]-4-(trifluorométhyl)pyrimidine-5-carboxamide,
le 2-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)pipéridin-1-yl]-N-(tétrahydrofuran-2-ylméthyl)-4-(trifluorométhyl) pyrimidine-5-carboxamide,
le N-cyclobutyl-2-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)pipéridin-1-yl]-4-(trifluorométhyl)pyrimidine-5-carboxamide,
le N-cyclopentyl-2-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)pipéridin-1-yl]-4-(trifluorométhyl)pyrimidine-5-carboxamide,
le N-[2-(1H-imidazol-4-yl)éthyl]-2-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)pipéridin-1-yl]-4-(trifluorométhyl)pyrimidine-5-carboxamide,
le N-(1-éthynylcyclohexyl)-2-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)pipéridin-1-yl]-4-(trifluorométhyl)pyrimidine-5-carboxamide,
leN-[(1R)-1-(hydroxyméthyl)2-méthylpropyl]-2-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)pipéridin-1-yl]-4-(trifluorométhyl)pyrimidine-5-carboxamide,
le N-(2-hydroxy-1,1-diméthyléthyl)-2-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)pipéridin-1-yl]-4-(trifluorométhyl) pyrimidine-5-carboxamide,
le N-(1,1-diéthylprop-2-ynyl)-2-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)pipéridin-1-yl]-4-(trifluorométhyl)pyrimidine-5-carboxamide,
le N-(2-hydroxy-1-méthyléthyl)-2-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)pipéridin-1-yl]-4-(trifluorométhyl)pyrimidine-5-carboxamide,
le N-[1-méthyl-2-(méthyloxy)éthyl]-2-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)pipéridin-1-yl]-4-(trifluorométhyl) pyrimidine-5-carboxamide,
le N-(1-méthyléthyl)-2-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)pipéridin-1-yl]pyrimidine-5-carboxamide,
le N-(1-méthyléthyl)-2-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)pipéridin-1-yl]-1,3-thiazole-4-carboxamide,
le N-(1-méthyléthyl)3-(méthylsulfonyl)-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)pipéridin-1-yl]benzamide,
le N-[(1R)-1-(aminocarbonyl)-2-méthylpropyl]-5-chloro-6-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)pipéridin-1-yl]pyridine-3-carboxamide,
le 5-chloro-N-(2-hydroxy-1-méthyléthyl)-6-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)pipéridin-1-yl]pyridine-

3-carboxamide,
le, 5-chloro-N-(1,1-diméthylprop-2-ynyl)-6-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)pipéridin-1-yl]pyridine-3-carboxamide,
le N-(2-amino-1-cyano-2-oxoéthyl)-5-chloro-6-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)pipéridin-1-yl]pyridine-3-carboxamide,
le N-[(1R)-1-(aminocarbonyl)-3-méthylbutyl]-5-chloro-6-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)pipéridin-1-yl]pyridine-3-carboxamide,
le N-[(1S)-1-(aminocarbonyl)-2-méthylpropyl]-5-chloro-6-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)pipéridin-1-yl]pyridine-3-carboxamide,
le N-[(1S)-1-(aminocarbonyl)-3-méthylbutyl]-5-chloro-6-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)pipéridin-1-yl]pyridine-3-carboxamide,
le 5-chloro-N-(1-méthyléthyl)-6-[4-(3-oxo-2,3-dihydro-4H-1,4-benzoxazin-4-yl)pipéridin-1-yl]pyridine-3-carboxamide,
le N-(1-méthyléthyl)-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)pipéridin-1-yl]benzamide,
le N-[(1S)-1-(aminocarbonyl)-2-méthylbutyl]-3-nitro-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)pipéridin-1-yl]benzamide,
le N-(1-méthyléthyl)-2-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)pipéridin-1-yl]-4-(trifluorométhyl)-5-pyrimidine-5-carboxamide,
le 3-chloro-N-(1-méthyléthyl)-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)pipéridin-1-yl]benzamide,
le 3-amino-N-(1-méthyléthyl)-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)pipéridin-1-yl]benzamide,
le N-(1-méthyléthyl)-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)pipéridin-1-yl]benzamide,
le N-[(1S)-1-(aminocarbonyl)-3-méthylbutyl]-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)pipéridin-1-yl]benzamide,
le 3-(éthylamino)-N-(1-méthyléthyl)-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)pipéridin-1-yl]benzamide,
le 3-(diéthylamino)-N-(1-méthyléthyl)-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)pipéridin-1-yl]benzamide,
le N-(1-méthyléthyl)-3-[(méthylsulfonyl)amino]-4-[4-(2-oxo-2H-3,1-benzoxazin-1(4H)-yl)pipéridin-1-yl]benzamide,
le 5-chloro-N-(1-méthyléthyl)-6-[4-(2-oxo-1,3-benzoxazol-3(2H)-yl)pipéridin-1-yl]pyridine-3-carboxamide,
le N-(1-méthyléthyl)-3-nitro-4-[4-(2-oxo-3,4-dihydroquinoléin-1(2H)-yl)pipéridin-1-yl]benzamide,
le 4-[4-(7-chloro-2-oxo-2H-3,1-benzoxazin-1(4H)-yl)pipéridin-1-yl]-N-(1-méthyléthyl)-3-nitrobenzamide,
le 5-chloro-N-(1-méthyléthyl)-6-[4-(2-oxo-3,4-dihydroquinoléin-1(2H)-yl)pipéridin-1-yl]pyridine-3-carboxamide,
le 4-[4-(2,2-dioxido-3,4-dihydro-1H-2,1,3-benzothiadiazin-1-yl)pipéridin-1-yl]-N-(1-méthyléthyl)-3-nitrobenzamide,

ou un sel ou un solvate pharmaceutiquement acceptable de celui-ci.

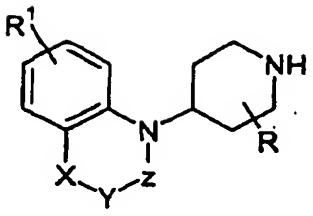
9. Composition pharmaceutique comprenant un composé selon l'une quelconque des revendications 1 à 8, en combinaison avec un diluant, un adjuvant ou un support pharmaceutiquement acceptable.

10. Composé selon l'une quelconque des revendications 1 à 8, destiné à être utilisé en thérapie.

11. Composé selon l'une quelconque des revendications 1 à 8, destiné à être utilisé dans le traitement de la polyarthrite rhumatoïde.

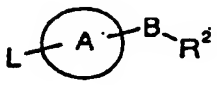
12. Utilisation d'un composé selon l'une quelconque des revendications 1 à 8 dans la fabrication d'un médicament destiné à être utilisé en thérapie.

13. Procédé de préparation d'un composé de formule (I) selon la revendication 1, **caractérisé en ce qu'**il comprend la réaction d'un composé de formule (II) :



(II)

dans laquelle R, R^1, X, Y et Z sont tels que définis dans la formule (I) ou un dérivé protégé de celui-ci, avec un composé de formule (III) :



(III)

dans laquelle B et R^2 sont tels que définis dans la formule (I) ou un dérivé protégé de celui-ci, et L est un groupement partant, et ensuite éventuellement dans n'importe quel ordre :

- la transformation de une ou plusieurs fonctions en d'autres fonctions
- l'élimination de tout groupement protecteur
- la formation d'un sel ou solvate pharmaceutiquement acceptable.